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THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 77 JUNE, 1957 No. 6

THE FAMILIAL OCCURRENCE OF PULMONARY ALVEOLAR MICROLITHIASIS*

By MERRILL C. SOSMAN, M.D., BOSTON, MASSACHUSETTS, GERALD D. DODD, M.D., HOUSTON, TEXAS, W. DUANE JONES, M.D., ASHLAND, KENTUCKY, *and* GEORGE U. PILLMORE, M.D., EASTON, PENNSYLVANIA

IN 1942, while in charge of the radiologic section of the Boston Induction Board, one of us saw a most unusual roentgenogram. It was a chest roentgenogram of a forty-five year old man showing both lungs filled by a fine sand-like mottling, obviously of calcium density. It resembled a snowstorm, or perhaps more correctly a sandstorm, almost obscuring the heart outlines and increasing in density from apex to base on each side. There was no similarity to miliary tuberculosis or, in fact, to any of the so-called miliary conditions previously seen and nothing to suggest either healed fungus infection or silicosis (Fig. 1). Later, we learned that the patient was completely free of symptoms, gave no history of occupational exposure, and showed completely normal responses to physical examination of his heart and lungs. We also learned that the patient had been roentgenographed by Dr. Sidney Morrison, of Boston, and subsequently at the Cushing Army General Hospital in Framingham, the Newton Hospital and the Faulkner Hospital in Jamaica Plain. He had been known to have this peculiar appearance in his chest roentgenograms for about five years preceding 1942. His roentgenograms were seen by most of the radiologists in and around Boston, but no one could make a definitive diagnosis or suggest a better name for the condition than the descriptive one of "pulmonary calcinosis" which Badger, *et al.*[1] attributed to Dr. Sidney Morrison. After several years of a completely symptom-free period, this patient gradually became dyspneic on exertion and eventually died late in 1951 following a final year of extreme pulmonary disability. Autopsy was obtained and the complete details are recorded in the case report by Badger, *et al.*[1] A summary of this case is included in this article (Case 1, Fig. 1–5).

* From the Departments of Radiology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts; the Department of Radiology, M. D. Anderson Hospital, Houston, Texas; the State Tuberculosis Hospital, District Four, Ashland, Kentucky; and the office of George U. Pillmore, Easton, Pennsylvania.

Presented in part before the Eastern Conference of Radiologists, Boston, Massachusetts, March 4, 1955; the Philadelphia Roentgen Ray Society, March 10, 1955; and the Eighth International Congress of Radiology, Mexico City, July 24, 1956.

Presented in detail before the Annual Meeting of the American Roentgen Ray Society in Los Angeles, California, September 25, 1956.

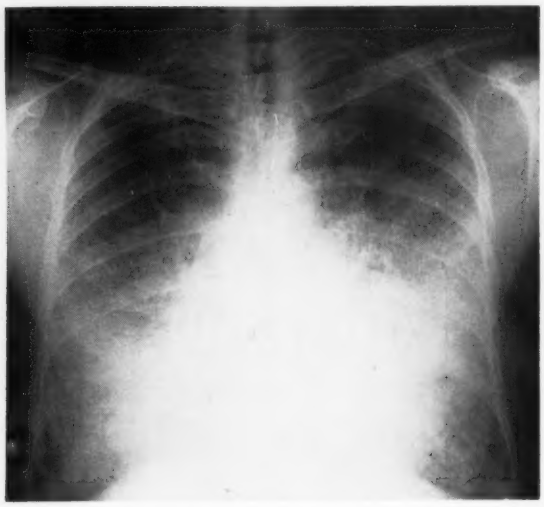

FIG. 1. Case 1. Roentgenogram of the chest taken January 30, 1942. The microliths are fine and discrete. The lungs otherwise appear normal. Patient asymptomatic.

The roentgenograms of a second similar case were brought to us by Dr. Perry Macgregor Knox, from the Moncton Tuberculosis Hospital, Moncton, New Brunswick, in the summer of 1942. They revealed what

FIG. 2. Case 1. Calculi in the left kidney and small calculi in the bladder and possibly in the prostate gland.

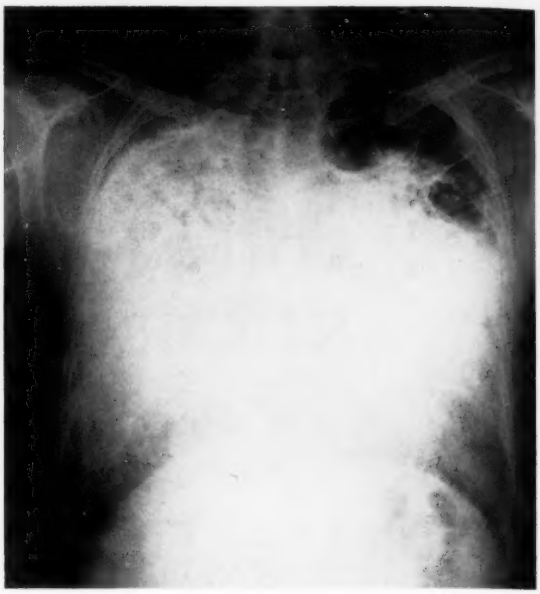

FIG. 3. Case 1. Chest roentgenogram taken December 7, 1950. Marked increase in calcium deposits. Extensive bullous emphysema in left apex. Patient now having severe pulmonary symptoms.

was immediately recognized as the same condition, *i.e.*, a fine diffuse pulmonary calcinosis, in a young male clerical worker of twenty-six, who had his first chest roentgenograms made in 1939 as part of an examination after induction into the Canadian Army. Although completely free of symptoms and perfectly normal to physical examination, he was rejected for military service because of the unusual chest findings in the roentgenograms. The details in

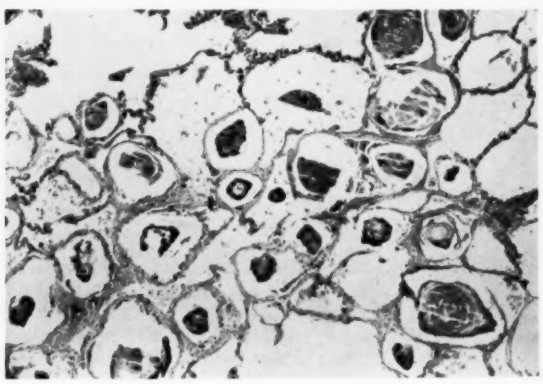

FIG. 4. Case 1. Histologic appearance in right upper lobe. Numerous concentrically laminated microliths in fairly normal alveoli.

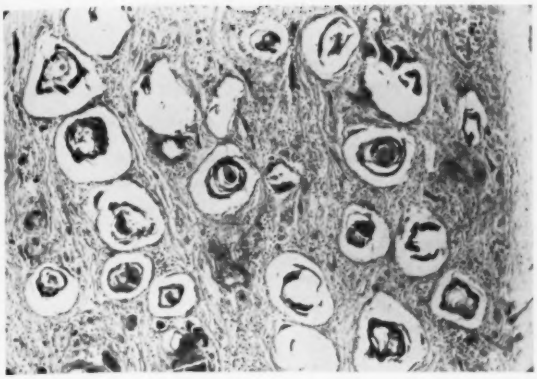

Fig. 5. Case 1. Dense fibrous tissue in lower lobe between alveoli, the walls of which are still fairly normal. All alveoli in this section contain calculi.

his case are given below as Case 2 and illustrated in Figures 6 and 7.

Several years later, in 1948, a graduate student in radiology, Dr. Gonzalo Esguerra-Gomez from Bogotá, Colombia, brought to us some chest roentgenograms of a young woman alleged to be thirty-two years old, later found to be forty years of age. These roentgenograms presented the identical appearance of fine grains of sand uniformly distributed throughout both lungs, but again more marked in the bases of the lungs and more in the medial than in the lateral portions, as would be expected from pure volumetric considerations. Overexposure was necessary to penetrate the dense calcific material. Bucky roentgenograms brought out the sharp contrast between the fine grains of calcium density in the bases of the lungs and the less dense liver, heart and abdominal shadows. The only history in her case was that "she lived by the edge of a dusty road." The details in her case are given in Case 3 below and illustrated in Figures 8 and 9.

We were able to tell Dr. Esguerra that we had seen the roentgenograms of two identical cases several years previously and had agreed to call the condition "pulmonary calcinosis," although we could not find any record of a corresponding condition in a casual search of the literature. None of us at that time had any idea as to the etiology of the disease nor, in fact, as to what the process in the lung was. We knew only that myriads of tiny spots or granules containing calcium were present.

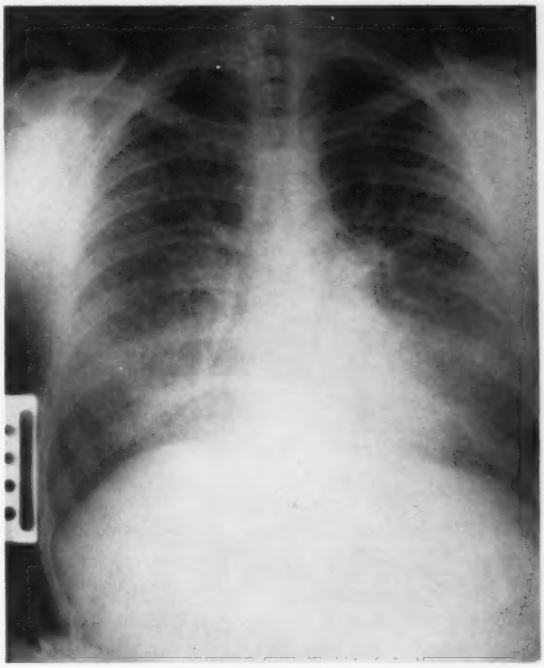

Fig. 6. Case 2. Roentgenogram of chest taken in 1941. The microliths are fine and discrete but they tend to be arranged in streaks along the blood vessels. Patient asymptomatic.

The next slow step along the trail of knowledge concerning this rare and esoteric

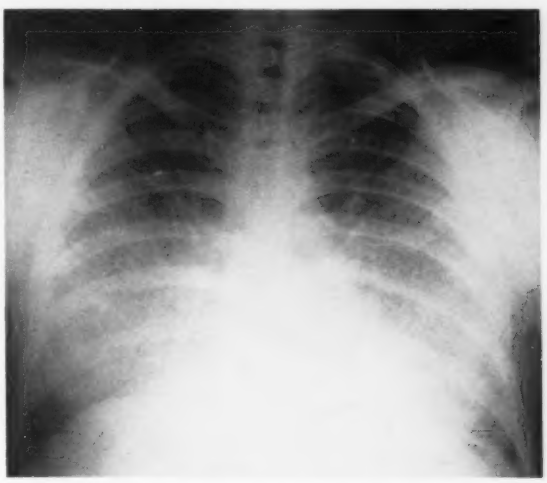

Fig. 7. Case 2. Four years later. Definite increase in pulmonary involvement. Patient still free of symptoms.

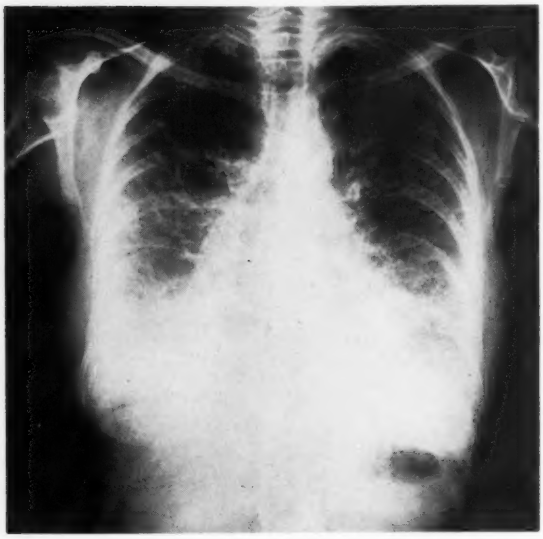

FIG. 8. Case 3. Roentgenogram of chest taken in 1948. Innumerable fine calcified deposits uniformly distributed throughout both lungs, some streaking along pulmonary vessels, and subpleural deposits. Patient asymptomatic.

disease turned out to be a misstep which led us away from the truth. This occurred during a visit from our good friend Dr. Peter Kerley of London in February, 1949. We showed him the roentgenograms of our first patient, calling it "pulmonary calcinosis," but Kerley insisted that the condition was really hemosiderosis, as he had seen an identical case which, on needle biopsy, was stated to be "hemosiderosis" by the pathologist.

We knew of the occurrence of pulmonary hemosiderosis in patients with severe mitral stenosis, particularly after repeated bouts of pulmonary congestion, and also of the rare case of idiopathic pulmonary hemosiderosis observed in young infants with bleeding tendencies, but neither condition resembled remotely the appearances seen in our patients with "pulmonary calcinosis." Kerley's case, however, was used to illustrate "hemosiderosis" in the textbook by Shanks and Kerley (Vol. II, p. 180, Fig. 179).[62] Interestingly enough, his patient eventually died in 1949, was autopsied and reported in detail by Sharp and Danino[18] and mentioned by J. Gough[3] from whom we received the thin gross section of the lung illustrated in Figures 14 and 15. But this came later in the series of contacts with this disease after we had learned what the basic histologic structure was like.

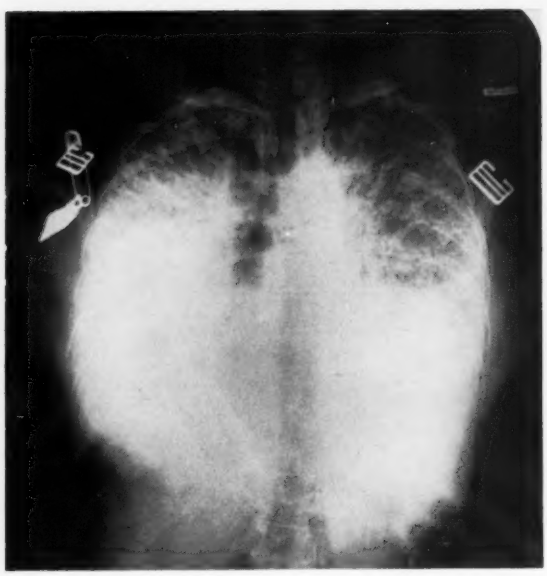

FIG. 9. Case 3. Chest roentgenogram eight years later revealing marked progression of the disease but the patient is still free of symptoms.

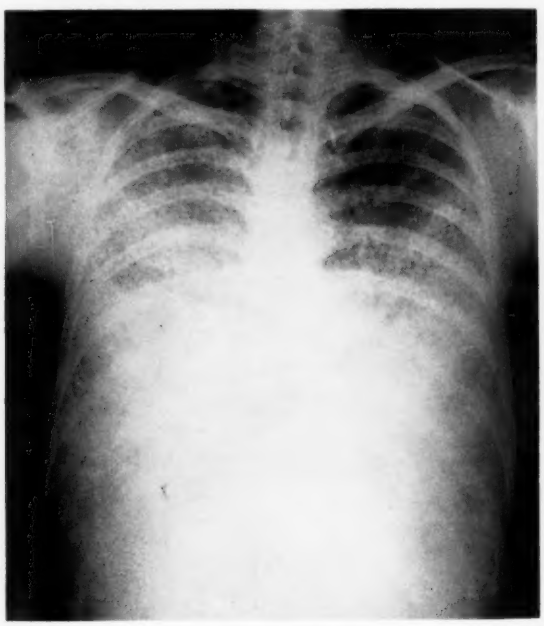

FIG. 10. Case 4. Chest roentgenogram taken September 8, 1954 revealing extensive involvement of both lungs in a man who had worked two years in and about a coal mine.

In the meantime, the patient of Badger, *et al.*,[1] Thomas B., was found dead at home on November 12, 1951, but we did not learn of the death nor of the autopsy until 1954. That summer another physician, Dr. John J. Pepper, visited Boston, bringing with him from Dr. W. Duane Jones, Director of the State Tuberculosis Hospital, District 4, in Ashland, Kentucky, the roentgenograms of three individuals all showing a most unusual condition. They asked if we could identify the disease or give them any leads concerning it. It took but a glance to realize that here was the same condition in different stages of development in a man and two women who turned out to be siblings! The man, thirty-seven years of age, had the more advanced degree of involvement and was having some symptoms of cough and shortness of breath on exertion. His two sisters, however, aged thirty-two and twenty-three denied any and all symptoms. The details of their records are included below as Cases 4, 5 and 6 (Fig. 10, 11, 12 and 13).

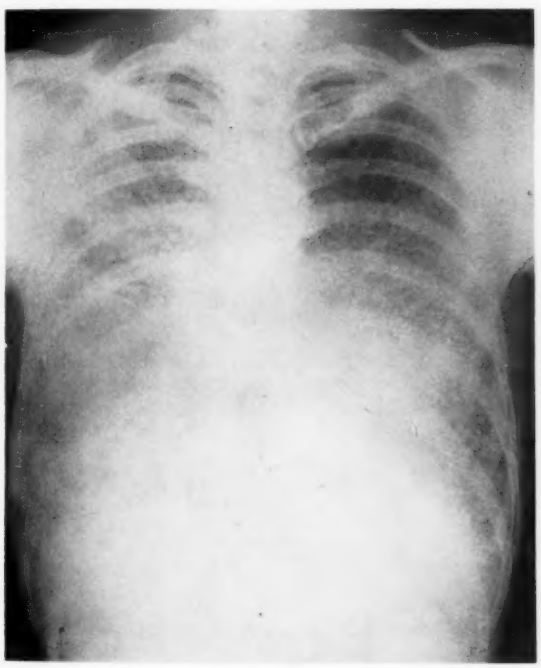

Fig. 11. Case 4. Pre-employment roentgenogram taken 10 years earlier (June 28, 1944) revealing a very similar type and degree of involvement. Patient was asymptomatic during most of the interval.

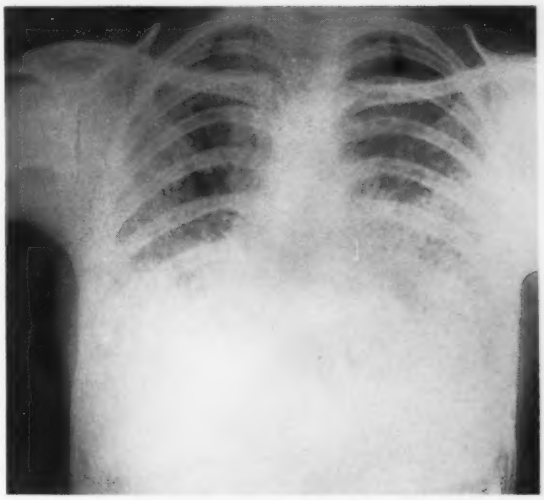

Fig. 12. Case 5. Routine chest roentgenogram of thirty-two year old sister of Case 4. Extensive involvement but no symptoms.

Here, for the first time in our experience, was a new clue to this disease—the fact that it could occur in three members of one family. This, of course, could mean that contact or contagion might play a part in its appearance or that environment, diet or even heredity could be important factors.

This sudden accession of cases stirred our

Fig. 13. Case 6. Routine chest roentgenogram of asymptomatic twenty-three year old sister of Cases 4 and 5.

FIG. 14. Roentgenogram of thin paper-mounted section (Gough[3]) of lung from Sharp and Danino's case.[18] Note the actual increase in the number of microliths in the lower lobe as compared with the upper lobe, and the accentuation of deposits along the interlobar fissure.

interest anew and led to a search of the literature, guided by the reference[18] given us by Mallory who originally identified the condition in the case of Badger, *et al.*[1] as "microlithiasis alveolaris pulmonum." During the search of the literature we found that it was Kerley's patient who was reported by Sharp and Danino[18] and we obtained a paper-mounted section of her lung through the courtesy of J. Gough, from Cardiff, Wales (Fig. 14 and 15).

Coincidence turned up again when an informal report of our findings in these 6

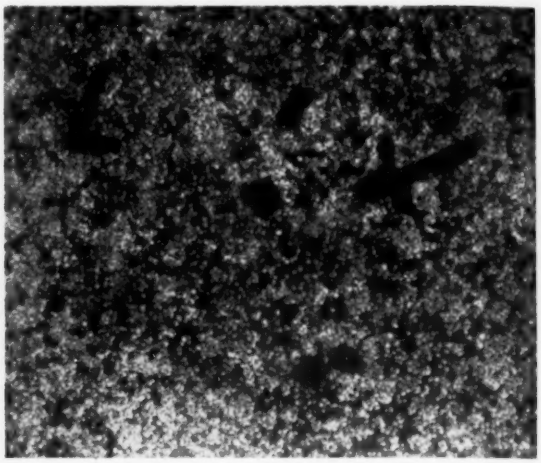

FIG. 15. Magnified section of roentgenogram in Figure 14 taken from area just below interlobar fissure. Note sharp outlines of individual calculi, variations in size and shape, and absence of coalescence.

cases was given before the Eastern Conference of Radiologists Meeting in Boston in March, 1955, and to the Philadelphia Roentgen Ray Society later that same

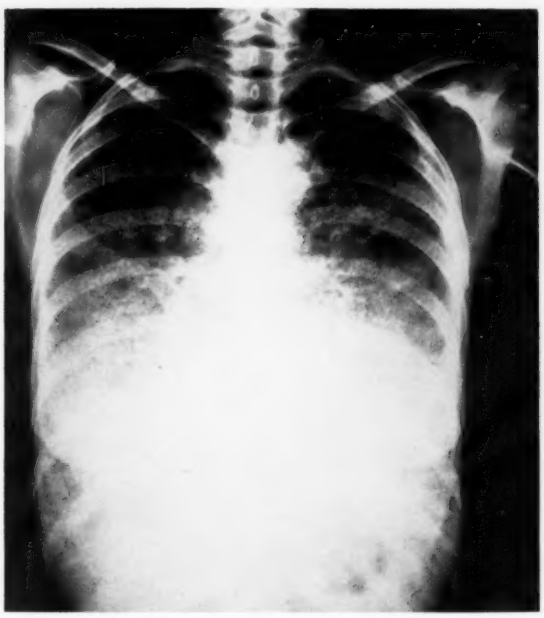

FIG. 16. Case 7. Roentgenogram of chest taken April 21, 1955 revealing diffuse fine calcific stippling throughout both lungs, obscuring outlines of heart and diaphragm. The calcium deposits in the base of the lungs can be seen through the upper abdominal shadows.

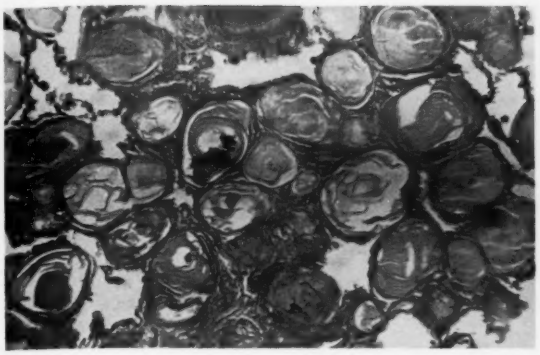

Fig. 17. Case 7. Biopsy of lung, high power, revealing concentrically laminated homogeneous calculi in most of the alveoli. Alveolar walls and septa were focally infiltrated, otherwise normal.

month. After the meeting Dr. George U. Pillmore of Easton, Pennsylvania, told us that he remembered an identical roentgenogram which he had exhibited at the Philadelphia Roentgen Ray Society Meeting several years previously, no one being able or willing to make a diagnosis. Learning of our 3 cases in one family, he decided to investigate the other members of his patient's family, with the result that 3 other sisters were found to have the same condition.

Fig. 18. Case 8. Photofluorogram of chest of thirty-nine year old sister of Case 7 taken before death, revealing fine sand-like mottling throughout both lungs, most marked in the bases. True condition recognized only by using the retrospectoscope.

Fig. 19. Case 9. Chest roentgenogram of thirty year old sister of Cases 7 and 8 taken June 17, 1955. Fine diffuse calcific stippling is seen throughout both lungs. Patient asymptomatic.

The original patient, in the meantime, was admitted to Jefferson Hospital, Philadelphia, where she was thoroughly studied, a lung biopsy confirming the diagnosis. One of the 3 sisters had died at the age of thirty-nine, her photofluorogram revealing the same condition before death (no autopsy) and the two other sisters aged thirty and forty-five were free of symptoms. All four of these patients are reported below as Cases 7, 8, 9 and 10 (Fig. 16, 17, 18, 19 and 20).

Dr. Paul Bishop of the Pennsylvania Hospital, Philadelphia, who heard the preliminary report noted above, sent us the roentgenograms of the eleventh new patient, a colored man of thirty-one whose history is included as Case 11 (Fig. 21 and 22). This is the first known case in a Negro, and the only one in this series with a history of occupational exposure, which is thought, however, to be of no etiologic significance.

The twelfth case was turned up in answer to a request for more information about the present condition of Case 2, and the pulmonary status of the other members of his family. Dr. Knox wrote that a brother of this patient was known to have the same

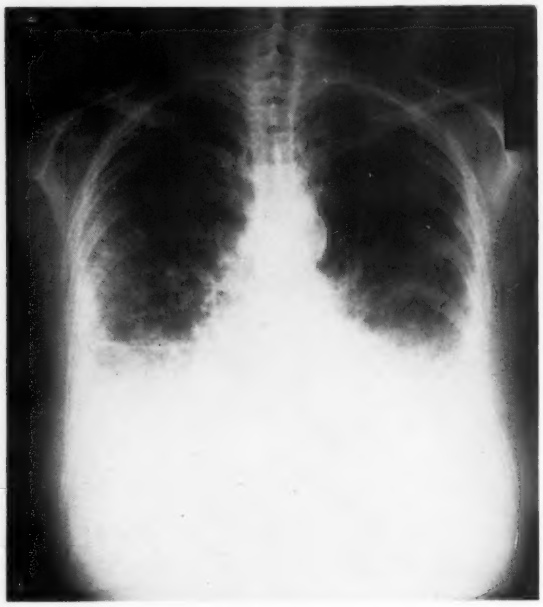

FIG. 20. Case 10. Routine chest roentgenogram of forty-five year old sister of Cases 7, 8 and 9 taken July 12, 1955, revealing extensive involvement of both lungs, most marked at the bases and obscuring outlines of heart and diaphragm. Completely asymptomatic at that date.

stippled appearance in his lungs. This has been verified by roentgenograms made in 1944 and also by recent roentgenograms in 1956. The details of this case, which represents the third instance of familial occurrence in the present series, are given below under Case 12 (Fig. 23 and 24). Investigation of the other members of the family has so far revealed no further occurrence of pulmonary calcinosis. The father, mother, 5 brothers and 2 sisters have all had recent chest roentgenograms and all have been judged to be free of microlithiasis.

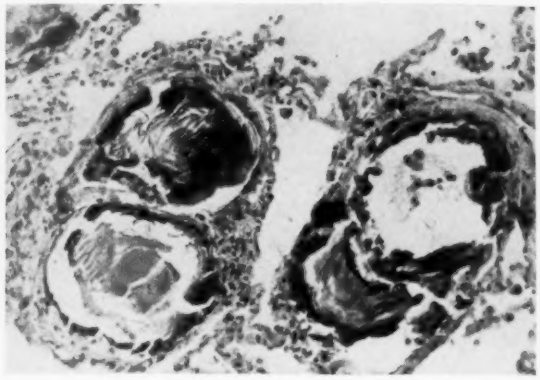

FIG. 22. Case 11. Biopsy of lung (high power). Laminated calculi in alveoli with considerable infiltration and fibrosis of stroma. Islands of metaplastic bone formation were also found without constant relationship to the microliths.

The thirteenth case is that of a twenty-eight year old female who died in March,

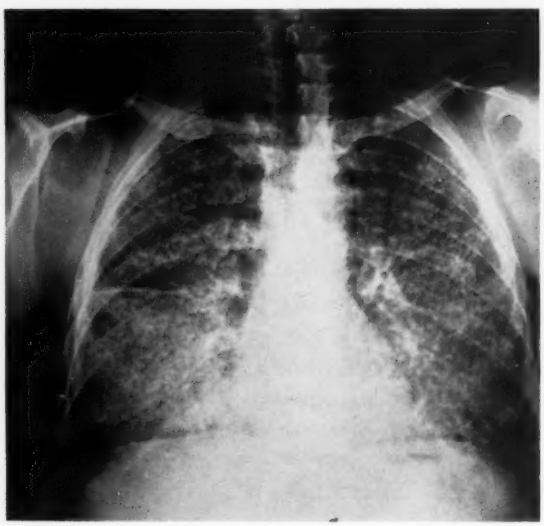

FIG. 21. Case 11. Bucky roentgenograms taken October 19, 1955 of thirty-one year old colored male who had pulmonary symptoms but negative physical examination. Known duration 12 years. Confirmed by biopsy.

FIG. 23. Case 12. Brother of Case 2. Routine roentgenogram of chest taken October 27, 1944 of asymptomatic nineteen year old recruit. Physical examination completely negative.

1952. A paper-mounted section of her lung was sent to us by Dr. J. Gough. The histologic examination, the sandpaper feel of the surface of the section and the roentgenogram of the section are all characteristic of microlithiasis. The details are reported under Case 13 and illustrated in Figure 25. As far as we know, this patient has not been previously reported, and permission to include her in this series has been given by Dr. Gough.

The fourteenth case was detected by Dr. Gonzalo Esguerra-Gomez in response to questions and requests about the condition of his first patient (Case 3) and the possible pulmonary involvement of other members of her family. This single lady of forty-six is the sister of Case 3, living in Santander, Colombia, and has no symptoms or signs of any pulmonary disease or disability. She submitted to roentgen examination of her chest only because of our requests through Dr. Esguerra. Much to everyone's surprise the roentgenogram (Fig. 26) revealed extensive calcification of both lungs. Details are given below under Case 14.

The fifteenth patient chronologically to be discovered with this disease was found by Dr. David H. Waterman of Knoxville, Tennessee, who brought the roentgenograms of "an unusual pulmonary condition" to one of us during a medical meeting in Boston. The condition was immediately recognized by Dr. E. B. D. Neuhauser as pulmonary microlithiasis. Dr. Waterman has given us permission to include the history and detailed findings of his patient. These are given below under Case 15 and illustrated in Figures 27 and 28.

Fig. 25. Case 13. Roentgenogram of thin paper-mounted section of lung (Gough's case 12,795-52) showing uniform distribution of microliths through upper lobe. Most of the calculi have fallen out of the lower lobe.

Fig. 24. Case 12. Same patient as in Figure 23, eleven years later. Roentgenogram suggests worsening but patient is still asymptomatic.

The chest roentgenograms of the sixteenth patient were sent to us by a former resident in radiology, Dr. James Sieniewicz, of Montreal, Quebec, after he had heard us discussing the condition, which was new to him, and after he had seen some of our roentgenograms of similar patients. The immediate reason for discovery of the pulmonary condition in his patient was a routine chest roentgenogram taken as part of an examination for life insurance, but it was subsequently learned that the abnormal pulmonary shadows had previously been

FIG. 26. Case 14. Sister of Case 3. Anteroposterior roentgenogram of chest revealing diffuse fine calcific deposits throughout both lungs obscuring heart and diaphragm. Lesions are coarser than in the sister's lungs. Emphysema is present in the left apex. Patient is asymptomatic.

FIG. 27. Case 15. Chest roentgenogram, taken May 1, 1955 of fifty-two year old female, showing the most advanced calcification in our series. Patient is working regularly without discomfort. The known duration is 13 years.

noted in 1942 in the British Air Force. Details in this case are reported below as Case 16 (Fig. 29).

The roentgenograms of the seventeenth patient were found, after considerable search, in the files of the Massachusetts General Hospital X-Ray Department. Dr. Richard Schatzki told us after hearing the preliminary report on this condition that he had seen films of a similar case in the teaching files at the Massachusetts General Hospital. We assumed that the ones he had seen were those of Case 1, but when we came to re-study his records, found that no roentgen examination of his chest had been made during that admission. Eventually, under Dr. L. L. Robbins' direction, strict search was made and the films of a different patient with the same disease were found. These had been seen and interpreted by Dr. George W. Holmes in 1931 as "pulmonary calcinosis," the first use of the term as far as we know at present. Details of this case are given below under Case 17 (Fig. 30).

The eighteenth case was also turned up by one of us (G. U. P.) as a result of a thorough search of old records. There was a constant but vague recollection that another similar chest film had been seen

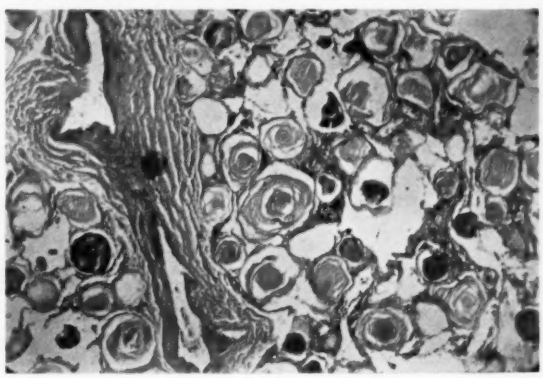

FIG. 28. Case 15. Biopsy of lung. Concentrically laminated "calcospherites" in 90 per cent of the alveoli, of variable size and possibly different ages. Only mild cellular infiltration and fibrosis. Alveolar walls mostly normal.

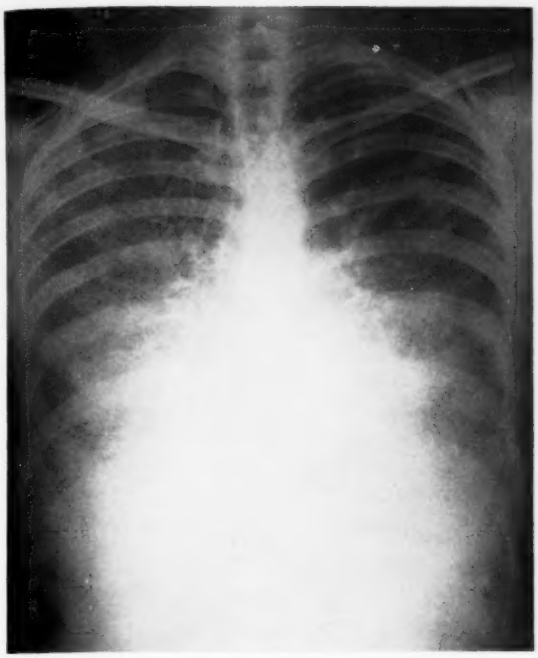

Fig. 29. Case 16. Roentgenogram dated October 19, 1955 of thirty-five year old male revealing characteristic fine sandstorm mottling in both lungs. Patient completely asymptomatic. Known duration 13 years.

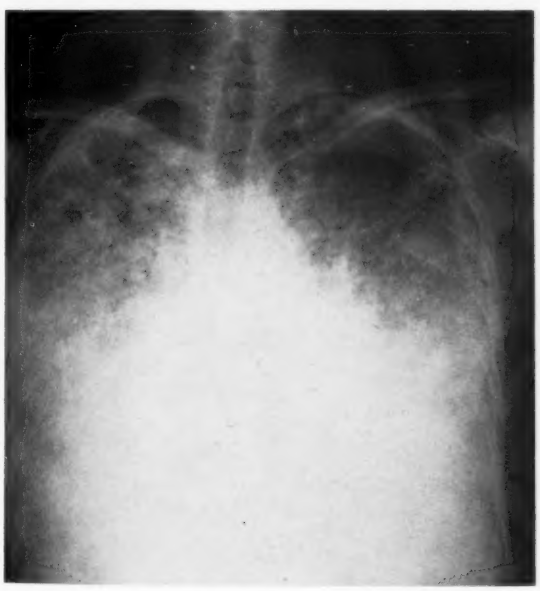

Fig. 30. Case 17. Roentgenogram taken April 13, 1931 of thirty-nine year old Armenian male, revealing diffuse and severe involvement. Patient has had symptoms for 2 years.

Fig. 31. Case 18. Chest roentgenogram taken March 28, 1932 of female school teacher about forty-five years of age, revealing extensive calcific deposits through both lungs. Patient's symptoms suggested asthma.

years ago, analyzed and discussed and then filed away in some safe place for future reference. As so often happens, the place was forgotten but on a visit to his summer camp the author found a box of records in the attic of the garage, mostly lantern slides and 5×7 inch positives of interesting cases. Among them were the copies of the films—another classical case of microlithiasis, discovered but not identified in 1932. Details of this case, as far as available, are reported below in Case 18 (Fig. 31).

The nineteenth case was originally seen by Dr. Howard Barkley of the M. D. Anderson Hospital and a pulmonary biopsy was done at another hospital, but no definite diagnosis was established. Subsequently, the patient came under the care of Dr. Kleberg Eckhardt of Corpus Christi, Texas, who eventually made the correct diagnosis after reading the article by Badger, *et al.*[1] The roentgenograms and microscopic slides of the biopsy material were sent to us by

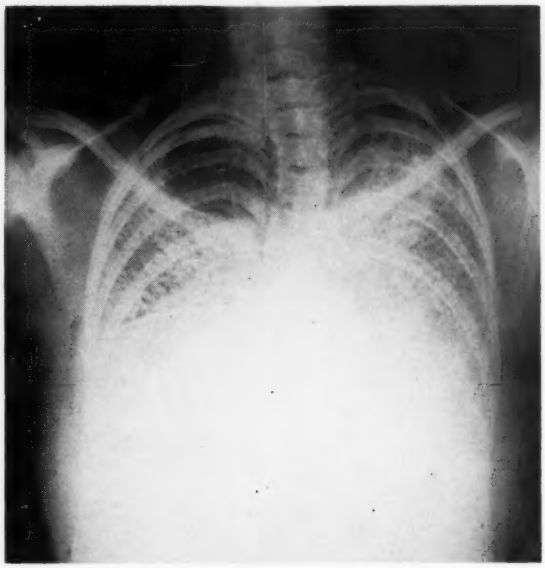

FIG. 32. Case 19. Bucky roentgenogram of chest taken June 27, 1956 of twenty-six year old Mexican female, revealing coarse nodulation and calcific stippling throughout both lungs. Patient has dyspnea on exertion.

Drs. Barkley, Daily and Eckhardt with permission to include the details in our report, although they plan to publish the case later in another journal. See Case 19 (Fig. 32 and 33) for details.

Cases 20, 21, 22, 23, and 24 were turned up as a result of talks and exhibits on this subject in Mexico City and in Los Angeles in 1956.

The twentieth case came from Winnipeg, Manitoba, through Dr. Arthur E. Childe, who sent us the roentgenograms and a clinical summary with an abstract of the autopsy record in the case of a sixty-six year old white male. The details will be found below under Case 20 (Fig. 34). The roentgenograms in this case were seen by many physicians over a period of years, but no one could make the correct diagnosis. (This case may be reported independently by Drs. Penner and Cherniak.)

The twenty-first case came from the Memorial Hospital, West Chester, Pennsylvania, through Dr. J. Stauffer Lehman of Philadelphia, from Dr. Peter Galamaga. The diagnosis was uncertain at first, later established by pulmonary biopsy. The patient was a fifty-two year old woman. Further details are given below under Case 21 (Fig. 35 and 36).

The twenty-second and twenty-third cases were found in California, and are those of a brother and sister, making the

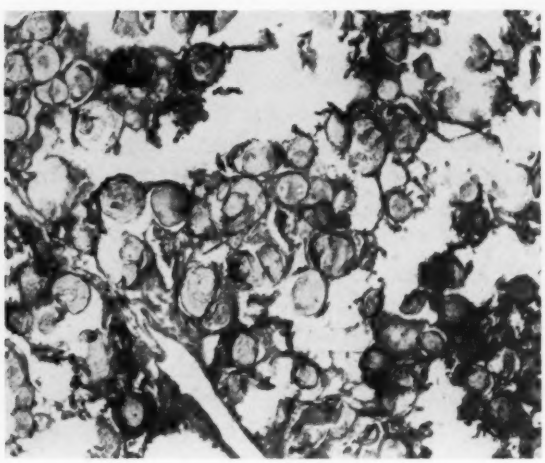

FIG. 33. Case 19. Biopsy of lung, ×70, revealing oval concentrically laminated microliths in most of the alveoli. Considerable cellular infiltration and more fibrosis than in others at this age.

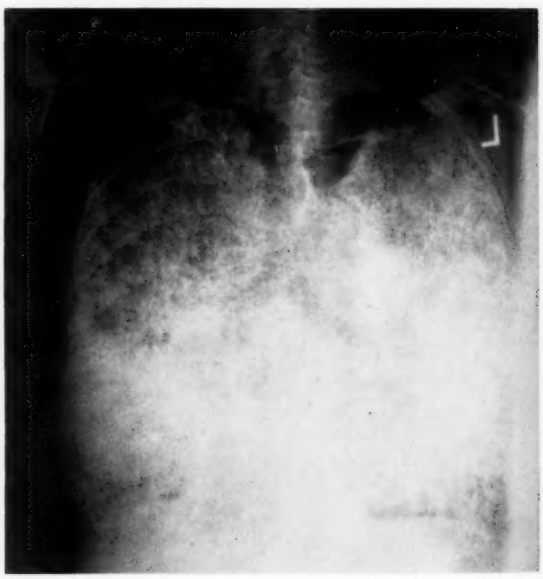

FIG. 34. Case 20. Roentgenogram of the chest dated June 20, 1952 demonstrating classical microlithiasis, also emphysema in left apex, and clear mediastinal zone.

Fig. 35. Case 21. Bucky roentgenogram of the chest, showing innumerable fine diffuse calculi, bullous emphysema of left apex, and concentrated deposits along bronchovascular tree. Note larger calcified nodules in spleen.

fifth example of familial incidence in this series. The chest roentgenograms and clinical details were sent to us by Dr.

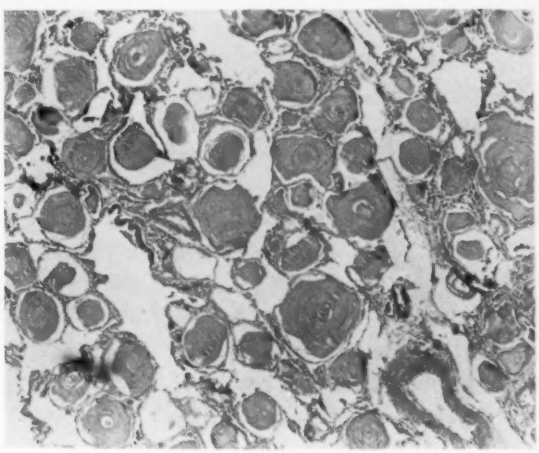

Fig. 36. Case 21. Biopsy of lung (×60), demonstrating laminated calculi filling many of the alveoli.

Fig. 37. Case 22. Roentgenogram of chest dated May 20, 1948, presenting classic snowstorm appearance. Particles are all of calcific density. Heart diaphragm, pleura and thoracic cage normal.

William O. Fricke and Dr. Donald R. Laing of Pasadena, California, after seeing our exhibit in Los Angeles. Details as far as available are given below under Case 22 (Fig. 37) and Case 23 (Fig. 38).

The twenty-fourth case came from Dr.

Fig. 38. Case 23. Routine chest roentgenogram of brother of Case 22 at age thirteen. Patient completely asymptomatic and physical examination negative.

B. P. Anderson Stuart of Sydney, Australia. Knowledge of the existence of this case was obtained through Dr. Whitmer Firor of Baltimore, who saw the roentgenograms when in Sydney during the war. At that time he was asked to bring them back to the United States and find out, if possible, what conditions they represented. He was unable to find anyone who knew the answer and filed the films for future reference. When he saw our exhibit in Los Angeles, he immediately recognized the condition as identical with that which he had seen in Australia, but after returning home was unable to find the films which had been filed ten years before. We wrote to Dr. Anderson Stuart who fortunately had other films of the patient which he sent to us. Further details are given below under Case 24.

Two other unpublished cases of this esoteric disease are known to exist, one verified by biopsy, but the material is not available for inclusion with the preliminary report, the first in American radiologic literature concerning this intriguing condition. No doubt other cases will come to light as soon as attention is called to the characteristic appearances in roentgenograms.

This makes an amazing total of 26 patients with this rare and unusual pulmonary condition seen by the authors, 23 of them hitherto unpublished. Four of them have been confirmed by autopsy (1 case of Badger, *et al.*, 2 cases of Gough and 1 case of Childe), 5 by biopsy (Cases 7, 11, 15, 19, and 21), 2 cases are dead without biopsy or autopsy (Cases 8 and 24) and the others are verified so far only by the characteristic roentgenograms. These all present the same appearance of diffuse sand-like or granular opacities spread uniformly throughout both lungs, often obscuring the cardiac outlines, the diaphragm and the normal vascular makings in the lungs. The density of the opacities is that of calcium and this must be emphasized in order to differentiate this condition from the miliary diseases which may simulate it, particularly in a light or underexposed roentgenogram. In a well-advanced case of pulmonary calcinosis an overexposed or overpenetrated roentgenogram is necessary to bring out detail in the lungs and to uncover some of the underlying structures. An exposure of 3, 4 or even 5 times the usual amount may be necessary to obtain good diagnostic roentgenograms.

This striking type and degree of pulmonary involvement is all the more remarkable when considered in contrast with the paucity or even total absence of clinical signs and symptoms. Most of the cases so far recognized have been discovered not because of pulmonary symptoms but accidentally during more or less routine roentgen examination of the chest such as for induction into the Armed Forces or surveys in a search for pulmonary tuberculosis. The only other condition presenting such marked pulmonary involvement with little or no pulmonary symptoms is sarcoidosis, but there the similarity ends. There is nothing to suggest that this condition is in any way related to sarcoidosis.

None of the patients in this series has had a history of adequate exposure to toxic materials (with the possible exception of Bishop's patient, Case 11). However, the distribution of the lesions, the roentgen appearance and the histologic findings would rule out pneumoconiosis even if the occupational exposure were suggestive. The only roentgenograms we have seen which show changes resembling this condition due to occupational hazards are those of men who have undergone prolonged exposure to metallic tin oxide. This was first noted by Hollis Potter of Chicago (personal communication), first reported in this country by Pendergrass and Pryde[52] and, recently, well documented in an excellent article by Robertson and Whitaker in the *Journal of the Faculty of Radiologists*.[55]

The lesions of stannosis, however, are coarser, of metallic density, and of a quite different distribution in the lungs than those of calcinosis. To one who is familiar with the roentgen appearance of both condi-

tions, there should be no difficulty in differentiating them even though the patients with stannosis are also said to be free of symptoms. The roentgenograms of patients with berylliosis[54] may simulate those of pulmonary microlithiasis at first glance, due to the fine diffuse nodularity of the lesions and a "ground glass" appearance as a background to the nodules. Again the differential maneuver is to obtain overexposed Bucky roentgenograms to bring out the calcific density. Lesions of berylliosis are granulomatous in nature and do not contain any metallic element or calcified particles. A careful history of occupational exposure is, of course, *de rigeur* in all patients who have diffuse pulmonary lesions.

Pulmonary hemosiderosis, particularly that form accompanying mitral stenosis and following repeated bouts of pulmonary congestion and hemoptysis, may cause greater difficulty in differential diagnosis. In fact, there has been actual confusion of the two conditions not only roentgenologically but also pathologically. The case illustrated in Shanks and Kerley's textbook, later reported by Sharp and Danino[18] and by Gough[3] is an excellent example of a mistake at the histologic level.

It is well known that hemosiderin deposited in the human lung causes relatively little reaction or fibrosis as compared to similar amounts of asbestos or silica. But nodules containing hemosiderin seem to attract calcium salts and in the advanced stages of hemosiderosis there may be many small and large deposits of calcium, some scattered through the lungs particularly at the bases, others in or around the hilar areas. By their gross characteristics and roentgen appearance they can easily be differentiated from pulmonary calcinosis.[30,43,48,50,57] Histologically, however, there may be a few concretions, even metaplastic bone formation, and these, associated with the changes of chronic passive congestion, possibly acute pulmonary edema, have been mistaken for pulmonary microlithiasis.[18] More will be said about this later in reviewing previously reported cases.

Considerable difficulty in differential diagnosis from roentgenologic studies, where practically all such problems now originate, may be encountered in the separation of this condition from the numerous types of miliary processes and diseases affecting the lungs. Miliary tuberculosis, miliary metastases, retrograde lymphangitic spread of metastases, diffuse capillary bronchitis, acute pulmonary edema (particularly from inhalation of toxic material), idiopathic pulmonary fibrosis (Hamman-Rich syndrome), chronic interstitial organizing pneumonitis, acute miliary fungus infections (blastomycosis, cryptococcosis, torulosis), lymphatic leukemia, pulmonary eosinophilic granulomatosis and even an occasional case of polycythemia may produce such diffuse and uniform lesions throughout both lungs, and so finely nodular in shape and distribution as to simulate pulmonary calcinosis. The answer to all of these is clear and simple, *i.e.*, the density of opacity of the individual lesions. This cannot be stressed too much. In cases of doubt an overexposed or overpenetrated Bucky roentgenogram will bring out the *striking calcific density* in pulmonary calcinosis, while all the others will give shadows of only soft tissue density.

It is quite conceivable, however, that there may be a stage in this condition in which only a noncalcified matrix fills the alveoli before the deposition of calcium and phosphorus salts occurs, which would, of course, give only shadows of soft tissue density and simulate any of the miliary infections or exudates. The cases of Friedreich[35–37] and of Benard, *et al.*[2] show only an intra-alveolar exudate, not laminated calculi. All 3 of Friedreich's patients died of typhoid fever and the pulmonary lesions must have been due either to capillary extravasations or possibly to acute pulmonary edema. Friedreich classified the lesions as "corpora amylacea" and there is no mention of calculi or calcification or stone formation. Unfortunately, in those days (1856) there were no roentgen rays available. Similarly, in the case of Munk[48] and Jona[43] the alveoli were filled with "amor-

phous material, for the most part sidero-calcific elements which are known as heart-failure cells." This is probably a combination of chronic passive congestion, hemosiderosis, and acute pulmonary edema or congestion. The roentgenogram of Munk's patient is typical of mitral heart disease with chronic pulmonary changes, both congestion and fibrosis, with numerous spots of variable size from pin point to coffee bean, and not at all suggestive of pulmonary calcinosis. Jona's case is quite similar. It cannot, however, be denied that there may be laminated precipitates in some alveoli, or "corpora amylacea" or even some real concretions, but the over-all picture is completely different. Munk's case and Jona's case are ones of rheumatic heart disease with mitral stenosis and secondary pulmonary changes related to the results of heart disease, while the real cases of diffuse alveolar microlithiasis are not associated with heart disease and pursue an entirely different course. Inclusion of such cases of mitral heart disease and hemosiderosis with those of microlithiasis only clouds the issues. It does, however, exemplify the fact that trees may obscure the forest. Or, because individual histologic lesions of identical nature occur in the lungs of two different patients, there is no reason to assume that the patient's disabilities and death are therefore due to the same disease. For example, the classic histologic lesions of sarcoid may be found in various situations and in diverse conditions, but all patients harboring sarcoid lesions do not have sarcoidosis. Wolbach taught that the sarcoid lesion was a specific histologic reaction which could be initiated by any one of several different inciting stimuli. Furthermore, we have previously learned[47] that a study of calcification in histologic sections will not suffice to predict whether there is quantitatively enough calcium to cast recognizable shadows *in vivo* in the roentgenogram. We contend, therefore, that the characteristic roentgen appearance should be considered an essential part of the clinical picture in the diagnosis of pulmonary alveolar microlithiasis or idiopathic pulmonary calcinosis.

We must, however, also consider in roentgenologic differential diagnosis the various diseases, usually infections such as tuberculosis or histoplasmosis, which result in numerous calcified foci through the lungs. These are easily and quickly separated from pulmonary calcinosis by recognizing the localized shot-like nodules of variable size and shape scattered irregularly through the lungs and often associated with calcified lymph nodes in the hila, mediastinum, neck or abdomen. The spleen and rarely the liver may show numerous small round smoothly-outlined calcified foci in histoplasmosis or tuberculosis, but so far we have seen calcified areas in the spleen in only one patient with pulmonary calcinosis (Case 21). The size, shape and distribution of the calcified foci following infection or focal necrosis in the human lung will immediately rule out the possibility of pulmonary calcinosis.

ROENTGEN APPEARANCE

The roentgen appearance of pulmonary alveolar microlithiasis is considered to be quite characteristic, and no other disease duplicates it or really even imitates it. There are, however, individual differences not only in the amount and degree of pulmonary involvement but also in the apparent size of the individual lesions, the simulation of coalescence, the amount of pleural or subpleural extension and the secondary changes such as emphysematous blebs. There are also changes and variations in the individual cases with the lapse of time. So far we have seen only progressive changes, occurring slowly but, nevertheless, constantly worsening until the lungs are almost completely filled by the calculi or the reactions to them, or both.

The patients may die by the actual smothering effect from the filling up of alveoli and the consequent loss of breathing capacity just as effectively brought about by this condition as may occur with pulmonary adenomatosis or even, more acutely

of course, by drowning. The alternative mode of death is by congestive heart failure (cor pulmonale) which is in turn due to the disease in the lungs and probably to increased pressure in the pulmonary circulation. We have records of pressures in the pulmonary vascular tree in two of these patients so far. In Case 7 intracardiac catheterization gave completely normal findings, and in Sato's[16] Case 1, intracardiac catheter measurements were also within normal ranges. Autopsies have failed to show any primary disease of the pulmonary vascular system but only secondary changes from the reactions and infections which resulted from the presence of innumerable foreign bodies.

The typical roentgen appearance can be described as a very fine sand-like mottling of both lungs, apparently uniform from apices to bases, but much denser at the bases because of the greater thickness (depth) of lung tissue at those portions. Individual lesions appear granular, sharp in outline, but irregular in shape, of calcific density, usually less than one millimeter in diameter and best recognized and appreciated by using a low-power magnifying glass (known locally in our Boston department as "The Cheater"). They may appear uniform in size but may seem to become larger and more irregular when they begin to crowd together later in the progress of the disease. The intervening spaces and the gross morphology of thorax, lung and chest are usually normal until later in the course of events. The cardiac outlines, hilar vessels and diaphragms are usually obscured by the total density of the microliths. In several cases the pleural surfaces were outlined by dense continuous deposits of calcium salts. This usually occurred, or at least was most evident, at the right base anteriorly and laterally. In other cases the entire pleural surface of each lung could be recognized as delineated by fine subpleural calcific deposits. Overexposed Bucky roentgenograms sometimes brought out the two smoothly outlined hard-shelled lungs leaving the mediastinal space between them as an area of lesser density in spite of its combined shadows of heart, vessels, and thoracic vertebrae. Similarly, the inferior borders of the lungs can be outlined through the liver and abdominal contents by the calcific density in lung and pleura which is more opaque than the liver, diaphragms and abdominal contents.

Only a few patients have been followed long enough to note and record the changes in the roentgen appearance which occur as the disease follows its inevitably progressive course. In Case 1 we have roentgenograms covering a period of nine years, and in Cases 4 and 12 of ten years. In the former the lesions became progressively denser, apparently coarser and more coalescent, and large emphysematous blebs developed in each apex. In Case 4 the evidence of worsening is less marked but still recognizable in the same manner of progression. In Case 12, however, there seems to have occurred a change which might be classed as improvement, but could equally well be explained on the basis of differences in technique, or by assuming that there was an infection or granulomatous process complicating the original roentgen appearance. (See Case 12 for a detailed discussion.) It seems to us that the amount and degree of change depend somewhat upon the age of the patient and the extent of involvement when the condition is first recognized. Thus in the patient of Manz,[10] where this condition was first observed in a girl of twelve years, there was said to be "no evidence of progressive change" after an interval of fifteen years. The woman died at thirty-seven years of age, a known duration of twenty-five years. On the other hand, our Case 3, aged forty when first seen, showed marked worsening of the pulmonary process at a second roentgen examination eight years later, Case 1 progressed to death in nine years and yet Case 16 is still completely free of symptoms at age of thirty-five after a known duration of fourteen years. Until the time when we identify the real beginning of this condition we can make no deductions as to its rate of devel-

opment nor as to its total duration. We know only that most of the cases are discovered in their twenties or thirties and they may die in three to twelve years. There must be a great deal of individual variation in intensity as well as in speed of development and progression. We do know, so far at least, that there is no apparent decrease or diminution of the condition as time goes on and no visible effect on its roentgen appearance by any form of therapy so far attempted.

REPORT OF CASES

CASE I

Thomas B.* was first seen by us in 1942, then aged forty-five, when his chest roentgenogram was shown to one of us at the Boston Armed Forces Induction Center. He had previously been working in a defense plant doing fairly heavy work assembling breechblocks for cannon, when a routine chest survey film revealed extensive pulmonary lesions of unknown character. Because of the roentgenographic findings and in spite of the fact that he had no symptoms, he was discharged and returned to his former occupation of part-time chauffeur and gasoline filling-station attendant. He gave no history of any pulmonary disease or difficulty except for a brief attack of pneumonia in 1937. Except for a tonsillectomy in 1912, his past history was negative. His family history was good except for one brother said to have died at the age of forty-six of cancer of the liver. He had been married twenty years, had 6 children, but had been separated from his wife for ten years.

His physical examination and laboratory tests in 1942, as reported by Dr. Badger, were all within normal limits. The blood cell counts and hemoglobin were normal, the urine was negative, the patch test for tuberculin sensitivity was negative, and the sputum was also negative for tubercle bacilli.

His chest roentgenogram, taken January 30, 1942 (Fig. 1) revealed an extensive, uniform, bilateral sand-like clouding of both lungs obscuring the cardiac outlines and the diaphragm, most marked in the bases and fading out toward the apices. Only in the apices could the intimate abnormal anatomic detail be appreciated, and then only with the help of a magnifying glass. This revealed myriads of tiny calcified particles, each one sharp, distinct and separate from the others, spread uniformly throughout all portions of the lungs. There seemed to be no fibrosis, scarring, shrinkage or distortion of the lungs, and no evidence of destruction, obstruction, caseation or cavitation could be made out. The total density of sand-like deposits was so great that it required an exposure of three times the average amount to secure a diagnostic roentgenogram.

We did not see the patient again but we did see roentgenograms of his chest from time to time at various clinics, film-reading sessions and seminars, always with the question, "What is it?" and always with the same answer, "We do not know, but someday we will find out. At present we call it 'idiopathic pulmonary calcinosis' for indexing purposes."

Dr. Badger was able to follow the patient from 1948 when he began to have definite symptoms of cough with mucoid sputum, weakness and shortness of breath on exertion, through an inexorably progressive downhill course, with marked loss of weight and increasing shortness of breath until his death on November 12, 1951. During the last four years of his life, extensive studies of his pulmonary functions, bronchoscopy, chemical studies of blood and urine and metabolic studies were done but yielded no clues as to the etiology or cause of the pulmonary calcinosis. His vital capacity decreased during this period and his alveolar arterial oxygen difference was four times greater than normal at rest. The other ventilatory studies indicated much better functional capacity than would seem possible from the amazing roentgenograms.

Summing up his final four years, it is important to note that bronchoscopy was negative, cytologic and cultural tests on the bronchial washings were negative, and no tubercle bacilli or fungi could be demonstrated by culture or guinea pig inoculation. In October, 1949, a large calculus was demonstrated in the left kidney (Fig. 2) and removed surgically. In 1950 a calculus was removed from his left ureter, but from then on he continued to pass small calculi, and roentgenographic examination demonstrated numerous small calculi in each kidney and in the suprapubic region, the latter possibly in the prostate. An analysis of the calculus removed was reported as "more than 60% ash, no phosphorus, uric acid or

* This patient has previously been reported by Badger, *et al.*[1]

cystine, and 4+ oxalate." His urine repeatedly showed oxalate crystals during this period.

Electrocardiograms were consistent with the presence of cor pulmonale but were otherwise non-contributory.

The metabolic studies were done under the direction of Dr. Fuller Albright and revealed essentially normal findings in serum proteins (6.5 gm. per cent), calcium (12.2 and 10.4 mg. per cent), phosphorus (3.0 and 3.2 mg. per cent), alkaline phosphatase (3.5 Bodansky units), nonprotein-nitrogen (40 mg.), chloride (99 mEq) and CO_2 content (20.4 mEq/l). A Sulkowitch test showed no elevation of calcium excretion in the urine.

Various attempts to alleviate the patient's symptoms and to change the course of his disease were made but with little success. He felt better while taking ACTH and cortisone but these did not affect the progress of his disease. Death was apparently due to pulmonary deficiency. Toward the end of his life he became cyanotic on exertion and developed moderate clubbing of his fingers.

Serial roentgenograms of this patient's chest from January 30, 1942 to December 7, 1950 were available for study and comparison, but only the first roentgenogram (Fig. 1) and the last one (Fig. 3) are reproduced here. The first roentgenogram (Morrison) showed that there was enough of the sand-like mottling to obscure the cardiac borders but not the diaphragm. The upper lobes were well aerated. The minor fissure on the right stood out sharply due to calcific deposits along the pleura. Both leaves of the diaphragm were low and slightly flattened. The second roentgenogram, November 3, 1944 (Cushing Hospital), showed an apparent increase in the amount and density of the pulmonary process but no other change. A third roentgenogram, January 14, 1948, showed still more extensive involvement, with some larger apparently coalescent areas and a spread into the apices and the extreme bases laterally. A fourth roentgenogram on January 24, 1949 at the Newton Hospital showed massive "conglomerate" areas in the right lower lobe, along the right chest laterally, and through most of the left lung. There was now marked deposition of calcium in the pleura over the left upper lobe and emphysematous areas through both lungs. The diaphragm, however, was still visible with fairly normal curves. The final examination on December 7, 1950 revealed an almost incomprehensible state of affairs in the lungs of a living, breathing patient. Both lungs were heavily calcified, with thick hard shells of calcium in or under the pleura and large irregular emphysematous bullae in the left upper lobe, less marked in the right apex. The character and extent of this amazing process is best shown by an overexposed Bucky roentgenogram (Fig. 3). It would seem from this roentgenogram that the only useful part of the lung remaining was the small portion in each base laterally, certainly less than 20 per cent of his original lung volume. There were no further changes demonstrated during the final year of his life.

The autopsy (BCH A-51-809) was done on November 13, 1951 and revealed both pleural cavities obliterated by dense adhesions. The lungs were much heavier and denser than normal (right 1,800 gm., left 1,500 gm.). They were cut with extreme difficulty and were of a gritty sensation. There was a marked bullous emphysema of both apices. Crystalline material lined some of the blebs and also was scattered throughout both lungs.

The heart was moderately enlarged, particularly the right ventricle, and weighed 480 gm., but was otherwise negative. The spleen, liver, gastrointestinal tract and gallbladder were unremarkable except for chronic passive congestion. There were no gallstones. The kidneys showed no gross evidence of either acute or chronic infection, but there were many small tan pebbles in the calyces of each kidney. Four parathyroid glands were identified and were normal except for slight hyperplasia. The brain was not examined. The gastric mucosa was normal.

Histologically a remarkable condition was found in the lungs. Approximately 80 per cent of the alveoli contained laminated concretions staining pink to bluish pink. In the upper lobes most of the alveoli were normal except for the concretions lying free inside them (Fig. 4). In the lower lobes there were foreign-body reactions in the alveolar walls and interstitial tissues, including giant cells, lymphocytic infiltration and interalveolar fibrosis (Fig. 5). Actual bone formation was not noted in the sections studied. There was no histologic evidence of tuberculosis or any other specific infection. The pulmonary vessels appeared normal.

Chemical analysis of a portion of the right lower lobe removed at autopsy was reported as noted in Table 1. On addition of hydrochloric

TABLE I

CHEMICAL ANALYSIS OF LUNG IN CASE 1

Total Solids	55.3 per cent
Moisture Content	44.7 per cent
Ash	34.4 per cent of fresh weight
	62.2 per cent of dry weight
Analysis of Ash	
SiO_2—trace	
P_2O_5—38.8 per cent	
CaO—51.8 per cent	
Fe_2O_3— 0.1 per cent*	

* Colorimetric estimate.

acid for solution of ash, the sample effervesced considerably, indicating the presence of carbonates in appreciable quantity.

This patient had 6 brothers and sisters and 6 children. Dr. Badger has been unsuccessful so far in finding any of them for study or for roentgenographic examination.

CASE 2

This male of English stock was twenty-five years old in 1942. The roentgenogram of his chest taken in 1941 was shown to one of us in 1942 and a duplicate left with us by Dr. Perry Macgregor Knox, of the Moncton Tuberculosis Hospital, Moncton, New Brunswick, who also furnished the information concerning this patient and his brother (Case 12) and gave us permission to include them in this report.

Herbert P., a bookkeeper from Chatham, New Brunswick, in perfect health, volunteered in 1939 for service in the Canadian Army. Routine roentgenograms of his chest after enlistment (Fig. 6) revealed a diffuse bilateral pulmonary condition, which, in spite of a completely negative physical examination, was considered of sufficient import to warrant rejection for service in the Armed Forces.

Past History. The patient was the eldest of 9 children, with an excellent family history. Several ancestors lived to the age of eighty or better and one to ninety-nine years. This patient had had the usual childhood diseases, mumps and measles but not whooping cough. There was no record of pleurisy or pneumonia, and no occupational exposure in mines or any dusty trade. No history of kidney or bladder trouble or of allergy could be obtained. There was a diagnosis of "mild typhoid" in 1936, which also affected his second brother at the same time.

His weight in 1939 was 150 pounds which rose to 175 and at times 185 in recent years. There was "stomach trouble" twelve years previously lasting about two years.

Chest roentgenograms of both parents were normal. Those of his 5 brothers and 3 sisters were normal except for the fifth sibling, a brother aged thirty, whose chest roentgenogram revealed a similar condition (See Case 12).

A chest roentgenogram of the patient, dated 1941 (Fig. 6), showed a very finely mottled diffuse process throughout both lungs, most marked in the bases medially and least marked in the apices where there was localized emphysema with slight calcification in the apical pleural caps. The lesions were minute, fine, sharply outlined, sand-like in appearance and obviously of calcific density. There was a definite exaggeration of markings radially from the hila, but no hilar or mediastinal masses, and no dilatation of the pulmonary vessels. The cardiac outlines were indistinct due to the pulmonary process, and, although appearing slightly enlarged to the left, the cardiac contour was normal. The diaphragm was sharply outlined and appeared normal in position and contour. The bones of the shoulder girdles and thoracic cage appeared normal in calcium content and in anatomic detail. The trachea and main bronchi were well visualized and appeared normal.

Comment. The roentgen appearance corresponds perfectly to previous cases of microlithiasis, but the process seems to be much less dense and with more normal lung remaining than in Case 1 when first seen. The difference may be due to an earlier stage of the condition, in view of the marked difference in the ages of these 2 patients.

A second roentgenogram of this patient's chest, dated May 16, 1945, showed a definite increase in the process, both in amount and density (Fig. 7). The cardiac outline was now almost completely obscured, the diaphragm was less distinct, and the upper mediastinal borders were obscured. The individual lesions, however, were still quite small, sharp and distinct, with no tendency toward coalescence or conglomeration. There was no increase in the apical emphysema. The third examination,

dated December 20, 1955 from Dr. E. Grenier, Gaspé, Quebec, was made with different technique and is difficult to compare with the 1941 roentgenogram. There was less inspiration, but the general appearance, quantity, distribution and density of the process all appeared unchanged, with no apparent progression since the 1945 roentgenogram.

At last report in December, 1955, he was in good health, but was short of breath on climbing. He was otherwise well and had not lost any time from work due to illness or disability since an appendectomy in 1937.

CASE 3

This is a female of Spanish descent. The roentgenograms of this patient's chest were brought to one of us by Dr. Gonzalo Esguerra-Gomez, from Bogotá, Colombia, who has given us permission to include this patient's history and roentgenograms in our report.

Elisa A., an unmarried woman aged forty in 1948 was born in Santander, Colombia and has lived there all her life "by the side of a dusty road." Twelve years ago she experienced severe abdominal pains with slight hematuria, suggesting renal colic. Since then she has had occasional abdominal pains. Her appetite was fair. There was no cough or fatigue. She has never worked in any industries or mines. The menses were normal. She did experience some weight loss.

The roentgenograms of her chest in 1948 (Fig. 8) revealed the classic appearance of pulmonary calcinosis, *i.e.*, innumerable very fine sand-like shadows of calcific density uniformly distributed throughout both lungs from apex to base. There was no sign of any other disease in the thorax, pleura, mediastinum, heart or lungs, and no distortion or abnormality of otherwise normal anatomic relationships except that the minor interlobar fissure on the right was definitely thickened and dense, probably due to heavy deposits of calcium salts. There were many thickened linear shadows extending radially from the hilar areas, seen and appreciated better in the upper lobes, extending in places to the extreme periphery of the lungs. These seemed to be due to calcific deposits along vessels or bronchi, possibly along lymphatics or septa. The cardiac outlines were almost completely obscured by the dense pulmonary process but the heart seemed to be enlarged both to right and left. The diaphragm was completely obscured. Numerous fine particles of calcium could be seen through the upper abdominal shadows, obviously representing deposits in those portions of the lung in the posterior costophrenic sulci. The bones all appeared normal in density and detail. There was a dense semilunar calcific deposit in or around the aortic knob.

Comment. This patient's process was well advanced, more extensive and quantitatively greater than in Case 2, and about equal to that noted in Case 1 in 1948 when he began to have symptoms at the age of fifty-one years.

The most recent roentgenograms of her chest, April, 1956, showed her lungs to be almost completely opaque (Fig. 9). The lower portions appeared solid and airless with only a little air content visible in the upper lobes. There was a narrow 2 cm. dark, clear zone in the midline of the chest from the base of the lungs up to the region of the carina, in which no calcium was demonstrable. The bones of the spine and thorax remained normal in density and detail. The pulmonary involvement seemed much worse than in the 1948 roentgenogram.

She returned for re-examination including roentgenography in April, 1956, at which time a more complete history, physical examination and laboratory tests were obtained. She was the second of 5 children. One sister had hypertension, the other siblings were said to be normal, but one sister who accompanied her, aged forty-six, was found to have a similar condition in her lungs. (See Case 14.)

The family history was unimportant. Her father died at the age of seventy-two of peritonitis. Her mother died of anemia following metrorrhagia. One brother, aged fifty, and 3 sisters, aged forty-six, forty-five and forty are living and claim to be well. None of them has any children. Two sisters and the brother have not yet been roentgenographed.

Past History: She had had the usual childhood diseases. Her general health has always been good except for the acute abdominal pain and hematuria noted above.

Physical Examination: Physically, she was well within normal limits except for an asymptomatic fibroid. No pathologic signs could be found in the chest. Roentgenograms of the abdomen were negative for urinary calculi.

Laboratory Data: Urine: Specific gravity 1.020; pH 5; no albumin or sugar. Blood: Serum calcium 4.9 mg. per cent (normal 4.2–5.1); cholesterol 190 mg. per cent; fasting blood sugar 80 mg. per cent; nonprotein nitrogen 31.2 mg. per cent; red blood cell count 5,600,000; Hb. 15.7 gm.; hematocrit 54 per cent; white blood cell count 8,000; differential blood count normal; sedimentation rate 39.0 mm. in one hour.

CASE 4

William C., a married white male of English descent, was thirty-seven years old in 1954. (The roentgenograms, case histories and clinical details of the next three patients, Cases 4, 5 and 6, were sent to us by Dr. W. Duane Jones and we are indebted to him for permission to publish them.) This patient was admitted to the State Tuberculosis Hospital in Ashland, Kentucky in 1954 because of cough, occasionally bloody sputum, and shortness of breath of about two years' duration, all of these symptoms having been brought out after a chest photofluorogram by a mobile unit indicated the need for further examination. The roentgenogram of his chest (Fig. 10) revealed the striking and unusual appearance of countless fine diffuse lesions of calcific density throughout both lungs. The possibilities of miliary tuberculosis or of some unusual fungus infection were considered.

Physical examination was remarkably unproductive except for rales in both bases, both front and back. His heart appeared normal in regard to size, position, rate, rhythm and sounds. Blood pressure was 115/80. The patient was fairly well nourished, did not appear ill, was not cyanotic, but had some clubbing of his fingers. There was no glandular enlargement. Nothing abnormal could be found in his abdomen.

His sputum was repeatedly negative on smear and culture for tubercle bacilli. Several specimens were examined for fungi but no pathogenic fungi were found. Candida albicans was found in one specimen. Complete blood cell counts were within normal ranges, sedimentation rate was normal, urinalysis and serologic tests for syphilis were negative. Tuberculin skin test with first strength PPD was 2+. Histoplasmin skin test and serum tests were negative.

Reviewing his past history, it was learned that he had been rejected by the army in 1943 because of a chest condition, but he was able to work without symptoms up until two years ago. He had coughed and raised sputum for many years. His past history recorded only the usual childhood diseases but no serious illnesses. His father, mother, 6 sisters and 6 brothers were all living and well. One uncle had died of tuberculosis, one sister was born dead and another sister died at the age of two years.

His occupational history indicated that he had spent most of his life as a hillside farmer in Knott County, Kentucky, but for a period of less than two years he worked about a coal mine, part of the time underground, and grinding bits part of the time. His total period of this employment was less than two years. It was further learned that he had undergone a pre-employment roentgenographic examination of the chest at that time, later found to be 1944. That roentgenogram was eventually located, studied and found to show almost the same degree of diffuse pulmonary calcinosis as in the 1954 roentgenograms (Fig. 11). This effectively ruled out any form of pneumoconiosis due to his work.

In the attempt to roentgenograph the chests of all members of the family, contacts of a possible contagious disease, it was found that two sisters aged thirty-two and twenty-three, respectively, had the same condition in their lungs but of less marked degree and intensity. Both sisters were free of all signs and symptoms of disease or disability. The father, mother, 6 brothers and 4 sisters and the patient's young son were subsequently roentgenographed with negative results.

The patient was afebrile and was discharged to his home. Arrangements were made for admission to the Louisville General Hospital where pulmonary function studies were done by Dr. Grover Sanders with the following results and conclusions:

Vital Capacity (*l.*)	
Observed	3.94
Predicted	3.86
Percentage of Predicted	102 per cent

Timed Vital Capacity (*l.*)	
One Second	62.5 per cent
Two Seconds	89 per cent
Three Seconds	94 per cent

Maximum Breathing Capacity (*MBC*)	
Observed	83.4
Predicted	104.2
Percentage of Predicted	80 per cent

Minute Ventilation (MV)

Resting—5.7 l./min./m.²	(normal (2.5–5)
Walking—9.6 l./min./m.²	(normal 8–11)

Arterial O_2 and CO_2

Oxygen Saturation	89.6 per cent
CO_2 Content	46.8 vol. per cent

Air Velocity Index—80/102–0.78

$$\textit{Breathing Reserve}\left(\frac{MBC - MV}{MBC}\right)$$

Observed	89.4 per cent
Normal	91–95 per cent

The total vital capacity is within predicted limits. There is very slight reduction in MBC and timed vital capacity which would be compatible with mild obstructive ventilatory insufficiency. The reduced O^2 saturation may be due to diffusion defects. However, further studies would be required to accurately evaluate this finding. Residual volume and total lung capacity were not done.

The patient refused pulmonary biopsy and was discharged to his home. At our request additional roentgenograms were made of his abdomen and urinary tract, but no calculi could be seen.

It was later learned that both of this patient's grandparents on his mother's side had died of supposed pulmonary tuberculosis "many years ago."

Reviewing his chest roentgenograms, dated June 28, 1944 (Fig. 11) and September 8, 1954 (Fig. 10), we note that there is a considerable technical difference between the two films, making it difficult to compare them with accuracy. The process was well advanced in 1944 when he was twenty-seven years of age, with very diffuse lesions, both fine and coarse, completely obscuring the cardiac outline and almost obscuring the diaphragm. The 1954 roentgenogram is technically much better with more penetration and more contrast. This film was given three times the amount of exposure which would normally be required to obtain a good roentgenogram. The lesions appear sharper and possibly smaller but more numerous. Small emphysematous blebs have appeared in both apices, which may be a poor sign prognostically judging from the course of events in Case 1. In both roentgenograms the bone detail and calcium content appear normal.

CASE 5

Nettie H. is a thirty-two year old married white female and sister of Case 4. Her chest condition was found on routine roentgenographic examination of family contacts. The patient had no symptoms, no disability, and refused hospitalization.

A chest roentgenogram, dated November 8, 1954 (Fig. 12), revealed extensive involvement of all lobes of both lungs to such an extent that the heart, diaphragm and all detail in the lower half of each lung were completely obscured. Here again the technical quality of the film is not good, being underexposed in view of the massive involvement. Through the partly aerated upper lobes could be seen coarse dense nodules and streaks spread uniformly on both sides, with some linear fibrous strands and emphysematous blebs in the apices. Many of the nodules contained sharp calcium particles, others appeared more fibrous. The aortic knob was obscured and the upper mediastinal boundaries were obliterated. The bones again appeared normal.

Comment. It seemed almost impossible that this patient could carry on normal activities and be free of symptoms with such extensive pulmonary involvement. The appearance suggested that the small lesions were coalescing like silicotic nodules do in progressing to the conglomerate stage.

CASE 6

Hettie H. is a twenty-three year old, married white female and a sister of Case 4. Her chest condition was also unexpectedly revealed by routine roentgenographic examination. This patient also denied symptoms, had no obvious disabilities but refused further study and hospitalization.

The roentgenogram of her chest, dated November 8, 1954, is technically better than the one of her elder sister although she was more obese. The roentgenogram (Fig. 13) revealed an extensive diffuse fine sand-like mottling uniformly distributed throughout both lungs. The heart outline and the diaphragm shadows were faint but appeared to be normal. The process was dense enough to obscure most of the intimate detail in the lower lobes, but in the upper lobes the individual lesions were found to be minute, sharp and of calcific density, with a tendency to be arranged in radiating streaks. No emphysematous blebs could be seen. The clavicles and ribs appeared normal and the trachea was also normal.

Comment. The appearance is characteristic of pulmonary microlithiasis probably in

an earlier stage than that of her brother and sister. Even so, it is remarkable that she had no symptoms and no disability in view of such extensive pulmonary involvement.

Reviewing the past history of the family as a whole, we find that William was the first child, Nettie and Hettie were the fourth and fifth children, respectively. No information as to difficulties in birth were obtained. All three were sick with measles at the same time, and all three had whooping cough, but not at the same time. None of them was known to have had diphtheria or any other serious respiratory disease.

William's abdominal roentgenograms showed no evidence of urinary calculi. No abdominal roentgenograms have been obtained on his 2 sisters as yet.

CASES 7, 8, 9 AND 10

The mother and father of these 4 sisters were married in Italy and came to this country thirty-eight years ago with one daughter (now Mrs. De S., one of the living sisters with microlithiasis) when she was about seven years old. The rest of the children, 3 daughters and 2 sons, were born in this country. The parents always resided in the same local community in this country until they died.

The mother died in 1940 at the age of fifty-one. For two years previous to her death she was partially paralyzed from a cerebral hemorrhage. She developed a high fever several days before her death and died without being hospitalized. She had never had a roentgen examination of her chest. Nothing else is known of her medical history.

The father died in 1942 at the age of fifty-two. He had been admitted to a local hospital January 5, 1942 for a cystoscopic examination. The records show that he was admitted at 8:30 A.M. and given general anesthesia at 9:30 A.M. for the procedure. As the cystoscopic examination was being made, he went into acute cardiac arrest and expired at 11:20 A.M. He had always been well and had never before visited a doctor. One of the daughters said that he had complained of pain in his abdomen for two days previous to his visiting the doctor. For many years he had worked as a laborer and as a bricklayer. Several years before his death he was a foreman for a local transit company. He had never had a roentgenogram of his chest taken. A postmortem examination was not performed. Nothing else is known of his medical history.

The father had a sister who is now living and well. She recently had her chest roentgenographed and it was found to be negative. Four of the mother's sister's children recently examined roentgenographically were found to have negative chests (3 male, 1 female). The mother's brother's chest recently roentgenographed was negative. The father's brother, about fifty-five years of age, recently showed negative roentgenographic findings in his chest. There are 2 living brothers of these 4 sisters with negative roentgenographic findings in their chests (ages forty and twenty-two).

There is a brother of the father now living in Italy and about sixty years of age with unknown findings in his chest. There are 8 immediate relatives of the father and mother in Italy who, we hope, will have chest roentgenograms taken later.

To summarize the family history: All of the 4 daughters of this man and wife are known to have pulmonary alveolar microlithiasis but not the 2 sons nor the father's brother or sister. Many descendants and relatives on the mother's side of the family have been roentgenographed in this country with no evidence of the disease being found.

CASE 7

The condition in the first sister's chest (Mary C.) was originally found in 1946 through a routine pre-employment chest roentgenogram. Other roentgenograms were subsequently taken but no clinical evaluation was made until 1952. A short history revealed her to be the wife of a soldier in the regular army who had been stationed at various posts in this country and abroad. Her only complaint at that time was that she was unable to become pregnant. She had been to see several doctors about this and had received several injections of her uterus and tubes to determine patency. Following one of these injections she had acute chest pain and was thought to have lipiodol emboli as noted below. In view of this history it was reasonable to suggest lipiodol emboli as a possible cause of the pulmonary densities.*

* It was subsequently discovered that her husband's oligospermia was probably the cause of her infertility. She did become pregnant in 1955, but as she neared term she went into labor, was admitted to the hospital and delivered a dead fetus. No sign

She was first seen clinically in May of 1952, then aged twenty-nine, with complaints suggestive of cardiospasm. A routine fluoroscopic screening of the patient's chest prior to an upper gastrointestinal series disclosed a generalized increase in density of the lungs. The cardiac silhouette was difficult to distinguish but no restriction of diaphragmatic motion was demonstrable and the examination of the esophagus, stomach and duodenum was within normal limits. Conventional roentgenograms of the chest demonstrated multiple minute shadows of calcium density throughout both lungs. The apices were relatively clear permitting visualization of the individual granules. These were sharply defined and the surrounding pulmonary tissues appeared devoid of inflammatory response. All were less than 0.5 mm. in diameter. The cardiac outline appeared normal.

Upon questioning, a history of mild exertional dyspnea was obtained. Recent ankle edema, cough, hemoptysis or chest pain were denied, but the patient was cognizant of easy fatigability. In 1945, while undergoing uterosalpingography, she had experienced sudden chest pain, hemoptysis and a low grade elevation of temperature. These complaints subsided in approximately one week. They may have been due to a lipiodol embolus. Subsequently she was aware of no subjective respiratory abnormalities until the gradual development of the present symptoms in 1951. However, approximately one month following uterosalpingography, a pre-employment chest roentgenogram first demonstrated the pulmonic densities. These were repeatedly noticed elsewhere on routine survey films, but diagnostic studies were not undertaken until 1952.

No past medical illnesses were recalled other then measles and mumps during childhood. In 1943 an appendectomy and right salpingo-oophorectomy were performed for septic disease and, in 1951, right nephropexy for low back pain and "pelvic pressure." These complaints subsided following surgery. The patient had lived in Tucson, Arizona, in 1945 and in Germany during 1950 and 1951.

Review of the systems revealed no pertinent findings. The menses were normal. Approximately 10 cigarettes were consumed daily and occasionally the patient drank small amounts of alcohol.

The physical examination was noncontributory save for slight hyper-resonance of the chest to percussion and distant heart sounds. Blood pressure was 110/78.

The family history, as interpreted at that time and as noted above, did not appear significant. One sister suffered from kidney disease and presumably died of coronary thrombosis at the age of thirty-nine (Case 8). A second sister, aged thirty (Case 9), suffered from an unspecified "allergy" and a third, aged forty-four, was living and well (Case 10). A thirty-four year old brother was in good health while a second brother was mentally retarded. Both brothers have negative chest roentgenograms.

The laboratory examination of the peripheral blood showed a red cell count of 5,080,000 with a hemoglobin of 14.7 gm. White cells totaled 7,250 with 58 per cent neutrophils, 39 per cent lymphocytes and 3 per cent basophils. The hematocrit was 48 per cent. Urinalysis was negative.

Blood chemistry: Urea nitrogen, 13.6 mg.; blood sugar, 66 mg. (fasting); serum calcium, 10.1 mg.; serum phosphorus, 3.1 mg.; serum phosphatase, 2.6 units (Bodansky); serum bilirubin, 0.4 mg.; protein bound iodine, 4.1 gamma per cent; plasma proteins, 6.57 gm. (total), 5.00 gm. (albumin), 1.50 gm. (globulin).

Wassermann and Kahn serologic reactions were negative. Smears and cultures of the sputum were negative for acid-fast bacilli as were gastric washings. The sputum was scanty.

Complement fixation titers for Histoplasma and Coccidioides were negative, for Blastomyces, 1:5. The collodion agglutination test for histoplasmosis was also negative.

On July 29, 1952, pulmonary function studies were performed by Dr. Hurley Motley. Vital capacity was 2,520 cc. (80 per cent of predicted normal). A vital capacity for three seconds from the beginning of expiration in the standing position equaled 2,154 cc. (69 per cent of predicted normal). Maximal breathing capacity was increased to 78 liters per minute imme-

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of fetal life could be obtained during labor. The fetus was disposed of before the interested physicians could obtain roentgenograms.

A serious complication ensued. Acute abdominal pain persisting after delivery necessitated abdominal exploration, which revealed infarction of the small intestine from mid-jejunum to cecum. This was resected and the jejunum was anastomosed to a cuff of terminal ileum. In spite of the odds against her recovery she recuperated slowly, gained weight and left the hospital in good condition two weeks later.

The infarction was due to herniation of the entire small intestine under an adhesion at the root of the mesentery, followed by volvulus at the root.

Her seriously compromised lungs did not handicap her appreciably in her battle against misfortune. The idea of hormonal deficiency as a substrate in her prolonged period of infertility and possibly in her microlithiasis has been discarded.

diately after one intermittent positive pressure breathing treatment with a bronchodilator drug indicating the presence of a slight degree of bronchospasm. Alveolar nitrogen after seven minutes of oxygen breathing equaled 1.9 per cent (the upper limits of normal 1.5 per cent) indicating the presence of a slight difficulty in the uniform distribution of air in the lung. Residual air volume was 1,415 cc., an increase of 29.8 per cent above the normal predicted value, representing 36 per cent of total lung volume and producing a slight to moderate degree of pulmonary emphysema. Ventilation factor equaled 64.6 per cent (normal 110 per cent or more). Arterial blood oxygen saturation was 97.1 per cent at rest and 96.4 per cent immediately after step-up exercise (both normal). Arterial blood CO_2 content was 41.7 volumes per cent at rest and 37.5 volumes per cent immediately after step-up exercise (normal). Resting arterial CO_2 pressure equaled 40 mm. Hg and arterial pressure 96 mm. Hg (both normal). The mean gradient of pressure for oxygen between the inspired air and alveolar air equaled 44 mm. Hg (normal 50 mm. Hg). The mean gradient of pressure for oxygen between alveolar air and arterial blood equaled 7 mm. Hg (normal). Plasma blood volume equaled 3,656 cc. (a decrease of 11 per cent from the normal predicted). Resting hematocrit equaled 38.7 per cent and step-up hematocrit equaled 38.7 per cent. The hemoglobin equaled 13.1 gm., based on the oxygen capacity at rest. The physiologic dead space equaled 103 cc. (normal) and the percentage tidal air effective equaled 72 per cent (normal). Oxygen in the amount of 4.03 per cent was removed from inspired air at rest and 5.10 per cent during step-up exercise (normal). Oxygen uptake at rest was normal and oxygen uptake during step-up exercise was 477 cc./min./m^2/BSA, (a very slight reduction from the normal predicted value of 500 cc. or more). Duration of dyspnea was 57 seconds after 30 step-ups in one minute.

Comment. The pulmonary function studies were interpreted as showing a moderate degree of functional impairment on the basis of the decrease in the timed vital capacity measurement, the slight increase in residual air volume and the slight increase in alveolar nitrogen after oxygen breathing for seven minutes. A slight to moderate degree of pulmonary emphysema was also present as indicated by a residual of 36 per cent of the total lung volume. The findings were felt to be consistent with early fibrotic changes in the lungs.

In view of the antecedent history of a lipiodol embolus and negative culture and sero-chemical studies, a tentative diagnosis of residual lipiodol droplets lodged within the pulmonary interstitial tissues was entertained. However, considerable doubt was cast upon this hypothesis by the work of Walther[68] who in 1939 had demonstrated that saponification and cellular absorption of lipiodol emboli readily occurred in the smaller arteries and capillaries of the lung. Circumstances prevented additional investigative studies at that time.

In November of 1953 the patient was re-admitted for comparative pulmonary function studies, pulmonary biopsy and cardiac catheterization. There had been no significant change in symptoms since the preceding admission and the physical findings were unaltered. Laboratory examination of the blood and urine remained essentially normal. Circulation times, employing ether and decholin, were respectively 5 and 12 seconds and the venous pressure 90 mm. of water. Roentgenograms of the chest showed no significant interval change upon comparison with the preceding studies.

Pulmonary function studies performed by Dr. John R. Griffith revealed the vital capacity (2,970 cc.) and the total capacity to be 100 per cent and 94 per cent of predicted value respectively. The residual volume was slightly increased (116 per cent of the predicted value). The ratio of the residual volume to the total capacity was slightly elevated, 32 per cent (predicted value 26 per cent). The index of intrapulmonary mixing was elevated, 2.95 following the breathing of 100 per cent O_2 for seven minutes as compared with a normal value of less than 1.5 per cent. The spirogram revealed no evidence of obstruction; however, some air trapping was present. Maximum breathing capacity was within normal limits, 85.1 liters per minute (97 per cent of the predicted value). The resting arterial blood was slightly unsaturated with O_2, 94.6 per cent (normal 96 per cent). Following one minute standard exercise the O_2 saturation fell to 92.5 per cent. No CO_2 retention was noted. Analysis of oxygen transfer gradients with 21 per cent O_2

and 16 per cent O_2 revealed no evidence of a diffusion problem.

Cardiac catheterization performed by Dr. Robert Johnson demonstrated the oxygen content of all vessels and chambers of the right side of the heart to be essentially the same. The arterial O_2 saturation was 91 per cent, the systemic blood flow 4.46 liters per minute with a cardiac index of 2.8 liters/minute/square meter. Pulmonary arteriolar resistance was found to be 1.6 (normal). No evidence of an intracardiac shunt was demonstrable and pressures in the pulmonary capillary bed, the pulmonary artery, the right ventricle, the right atrium and the superior vena cava were all within normal limits. Simultaneous electrocardiography was normal with no deviations from the preceding year's tracing.

At thoracotomy the pleural space was found to be free of adhesions and to contain a normal amount of fluid. However, the visceral layer was studded with numerous tiny eminences which originated in the underlying pulmonary tissue and imparted a "sandpaper-like" appearance to the pleural surface. The lung was extremely firm in consistency and cut with difficulty, a "gritty" sensation being described by the operator.

Microscopic examination of the hematoxylin and eosin stained sections of lung disclosed most alveoli to be occupied by oval, concentrically laminated masses of acidophilic acellular material (Fig. 17). This was isotropic and of homogeneous appearance except for occasional more deeply stained peripheral lamellae. Some lamellae, centrally and peripherally, were pale blue. Only one such structure was present in each alveolus involved and many alveoli were markedly expanded and completely filled by this material. Hemosiderin-laden macrophages were present in a few uninvolved alveoli. Septa were not thickened but these were slightly focally infiltrated by lymphocytes and plasma cells. Small vessels were not abnormal. Interstitial deposits of acidophilic substance were not identified.

Fat stains on all material were negative.

Comment. The elevated index of intrapulmonary mixing was considered indicative of some difficulty in the distribution of air in the lungs, a conclusion which correlated well with the microscopic demonstration of reduced capacity of individual alveoli by the centrally positioned calcific bodies. Although some progression of the process was denoted by the interval decrease in oxygen saturation of the resting arterial blood, this was not obvious clinically and the total lung volume and maximum breathing capacity had actually improved upon comparison with the 1952 studies. The slight degree of pulmonary emphysema indicated by the elevation of the residual volume and the increase in the ratio of residual volume to total capacity was not yet reflected in the pulmonary circulation as manifested by the normal intracardiac and pulmonary artery pressures.

Although the findings compiled during the second admission conclusively exclude lipiodol emboli as an etiologic factor, no conclusion was hazarded other than one of "intra-alveolar pulmonary calcification of unknown origin."

In April, 1955, the patient was re-hospitalized for additional investigation. Again, the symptomatology and physical findings were essentially unchanged and blood chemistries were normal. Additional studies, including basal metabolic rate, urine 17 ketosteroids and bromosulphalein test of liver function were also normal. The decholin circulation time remained 12 seconds, the venous pressure 94 mm. of water.

A complete roentgen study of the skeleton showed an apparently normal calcium content throughout. No renal calculi were demonstrable. Although concurrent roentgenograms of the chest suggested progressive opacification of the lungs during the one and one-half year interval (Fig. 16), repetition of the pulmonary function studies showed little change upon comparison with those of November, 1953.

Subsequent roentgenologic investigation of the patient's family was made possible through the efforts of Dr. George Pillmore. Both surviving sisters were found to have similar pulmonary changes and an antemortem chest roentgenogram of the deceased sister was identical in all respects.

Comment. The additional studies performed during this admission afforded no further information as to the etiology of the

pulmonary calcifications. No appreciable progression of symptoms was evident despite roentgen demonstration of increased calcium deposition over a four year period. Analysis of the serial pulmonary function examinations indicates gradual interference with alveolar gas distribution by the microliths and consequent depletion of the oxygen saturation of the arterial blood. The consistently demonstrated pulmonary emphysema is undoubtedly compensatory in nature, a correlative which at first seems to mask and later accentuate the respiratory disability. No abnormalities of gas diffusion are apparent.

CASE 8

The medical information concerning Mrs. Mary W. is limited. She died peacefully in her sleep at the age of thirty-nine in the spring of 1951. Her family physician reported that two or three hours before her death he had performed a cystoscopic examination of her at his office. The family had called him soon thereafter because she could not be aroused from her sleep on the sofa in the living room of her home. He remembered that she had had considerable respiratory difficulty the last several times that he had seen her. Arriving at the home he found her dead. The family told him that after she had left his office she had complained of difficulty in breathing and dizziness and had decided to lie on the sofa. There she promptly went to sleep. They could not arouse her for dinner.

The family physician recalled that she married a soldier during the war and that they were unhappy because she could not have a baby. He had told her that she was "all right" after establishing that her tubes were patent, and that her husband was "all right" too. She was overjoyed but three months later her husband was killed in France. She never remarried and after the war obtained employment in the local toy factory as "floor girl" but she gave it up later because of difficulty in breathing.

The family doctor had previously admitted her to a local hospital on July 2, 1950, with a diagnosis of left hydronephrosis which he had established by roentgenographic examination in his office following a retrograde study of the left side of the urinary tract. There was no evidence of urinary calculus. She gave a history of ten years of pain in the left side of her back and of headaches, dizzy spells, puffiness under the left eye, and spots before her eyes. There was difficulty of breathing upon exertion.

She had had the usual childhood diseases but no serious illness in the past. Tonsils and adenoids had been removed at the age of twenty-nine. Menses were regular and lasted one to three days.

The physical examination revealed a well nourished, well developed not acutely ill patient lying comfortably in bed with a blood pressure of 110/80. The superficial systemic review was negative.

Laboratory Data: Blood: Red cell count, 4,720,000; hemoglobin, 12.4 gm.; color index, 0.7; white cell count, 7,600; segm., 61 per cent; stabs, 3 per cent; juveniles, 4 per cent; eosinophils, 6 per cent; lymphocytes, 26 per cent. Urine: Albumin, negative; sugar, negative; specific gravity, 1.012; few threads of mucus; leukocytes, 7–10 per high power field; erythrocytes, 4–5 per high power field.

At the hospital she did not have a chest roentgenogram taken.

The surgeon operated on July 3, 1950 and through a left Mayo kidney incision approach found a left hydronephrosis caused by an anomalous vessel which was severed, and the usual routine was used in closure. Nothing unusual was found on the anesthetist's chart. On July 5, she had a temperature of 101, pulse 120, and respirations were 20. Thereafter she had an uneventful recovery and was discharged from the hospital on July 11, 1950.

The photofluorogram (70 mm. chest survey film) was obtained through Dr. M. C. Stayer, director of the Department of Health, Bureau of Tuberculosis Control at Harrisburg, Pennsylvania. The minifilm was dated May, 1951, and revealed unmistakable evidence of pulmonary microlithiasis. The process (Fig. 18) was less intense than in her sister, Mrs. C. (Case 7) although this patient was older, thirty-nine years, when she died. Details are hard to determine on the small film but a careful study using magnification showed the lower portions of the lungs so dense that the heart, diaphragm and costophrenic angles were completely obscured. This density gradually decreased toward the upper portions where the fine miliary lesions stood out sharply and distinctly, all of calcium density and with no coalescence or conglomeration. The vascular tree was faintly

visible around the hila. There were no cavities or emphysematous bullae and no evidence of other disease or abnormality. The bones, as far as seen, appeared quite normal.

CASE 9

Mrs. Viola V., aged thirty, is the youngest of the four sisters. She came with her sister, Mrs. C., when the latter was recalled in 1955 for further examination. When invited to have her chest roentgenographed she protested that it was unnecessary as she was perfectly well, but the roentgenogram (Fig. 19) revealed a well developed case of microlithiasis. This patient had a record of five admissions to local hospitals without once having a roentgen examination of her chest, so that there is no evidence as to how long her pulmonary condition had been present. During this period covering ages eighteen to twenty-nine she had no history of any respiratory disease or symptoms, and at the present age of thirty has no difficulty in breathing even upon exertion. She is married, and in addition to her regular household duties also has a job as a full-time machinist in a mill working at steady hours.

Her first admission to a local hospital at the age of eighteen was on January 27, 1944 with a diagnosis of acute appendicitis. The next admission was at the age of twenty-one for freeing of adhesions in the right iliac fossa. The third admission was on December 14, 1947 at the age of twenty-two with a diagnosis of suspected pre-eclampsia symptoms. Her fourth admission was February 14, 1948 for delivery of a full-term baby boy who incidentally, now at the age of seven years, is without roentgen evidence of pulmonary microlithiasis. Her last and fifth admission to the hospital at the age of twenty-nine was on July 22, 1954, with a diagnosis of endometriosis, erosion of the cervix, old laceration of both labia majora, rectocele, and perineal lacerations of long standing.

During the first admission on January 27, 1944 the patient had a spinal anesthesia administered (spinocain $1\frac{1}{5}$ cc.), and the operation lasted from 9:26 P.M. to 10:00 P.M. as an "acute suppurative appendix" was removed. At the time of admission the temperature was 99.3° F., pulse 70, respiration 20. The white blood cell count was 12,000, red blood cell count 4,130,000, hemoglobin 12 gm. (80 per cent), polymorphonuclears 88 per cent, and lymphocytes 12 per cent. The urine was negative for albumin, sugar, leukocytes, erythrocytes and casts. The specific gravity was not given. During her stay in the hospital until February 3, 1944, her temperature ranged no higher than 100°F. on the second day, and it subsided to normal on the eighth day. She was discharged as cured.

The second admission to the hospital was August 1, 1946. The diagnosis was abdominal adhesions, the anesthesia used was ether, and the operation was performed the day following admission. The adhesions were found and severed. The record shows a urinalysis negative for albumin and sugar, a reaction of pH 5, specific gravity 1.028 and normal blood cell counts. The patient was discharged after an uneventful convalescence ten days later.

At the time of the third admission to the hospital on December 14, 1947, the patient was seven months pregnant with suspected pre-eclampsia symptoms. She was discharged two days later with a diagnosis of "acute indigestion (dietary indiscretion)." On this admission she gave a history of chicken pox and measles, the two operations as described above and a tonsillectomy and an adenoidectomy in 1946. The family history was negative for tuberculosis, cardiac disease, respiratory diseases, malignancy and mental diseases. She had a negative Kahn and Kolmer test, Type A blood, and negative Rh factor. Her weight was 140 pounds. The systemic review was negative. The hemoglobin was 10.5 gm. (73 per cent), red blood cell count 4,220,000, white blood cell count 11,000, differential blood cell count normal. The urinalysis was again negative for albumin and sugar, specific gravity 1.008, pH acid. Her temperature was normal, pulse 70 to 80, respiration 20 and blood pressure 104/70.

The fourth admission to the hospital on February 14, 1948 was at full term pregnancy. The menstrual history was recorded with the onset at the age of fifteen. Thereafter, she had menstruated regularly every 28 days for three day periods until pregnancy. Nothing was added to the personal or family history not already disclosed. Her weight upon admission was 150 pounds. Again, the systemic review was negative, and the urine and blood studies approximated those already described. The temperature, pulse, and respiration were normal. The delivery was reported as normal on February 15, 1948 without forceps or episiotomy, and the placenta was reported as normal.

She was discharged from the hospital on February 21, with a "normal baby boy."

The fifth and last recorded hospital admission on July 22, 1954 at the age of twenty-nine was made under a diagnosis listed above in the summary of admission to hospitals. She remained in the hospital thirteen days. During this period she was under general anesthesia for two hours for the following operative procedures: Dilation and curettage, cautery of the cervix, repair of both labia majora, posterior colporrhaphy, perineorrhaphy, and resection of rectovaginal mass. Her respirations remained at 20 throughout the operation. Her temperature rose to 101° F. the day after the operation and her pulse rose to 110, but during her entire stay in the hospital her respiration remained at a peaceful 20. Several blood pressure recordings were made during her stay in the hospital with the highest at 120/98 and the lowest 108/80. The anesthetist had made a note that postoperatively the nurse should watch for hypotension. Blood and urine studies followed the patterns previously reviewed. Other recorded data, in addition to findings already listed, were hematocrit 43 per cent, urea 13.6 mg., glucose 114 mg. No other blood chemical analysis was made. Under "family history" was listed "a child, husband, and both parents living and well with no history of chronic disease in the family." Once again there was a negative systemic review previous to her operation. A roentgen examination of her chest had not been made, but she had had an intravenous urographic study and a barium enema examination of her colon, both of which proved to be negative. There were no abnormal abdominal calcifications. She was discharged from the hospital on August 4, 1954.

The roentgenograms of her chest (Fig. 19) dated June 17, 1955 revealed a normally developed thorax, heart and lungs, with the diaphragm normal in shape and in the position of deep inspiration. Both lower lobes, particularly the medial portions, were cloudy, due to a diffuse fine granular stippling which was uniform from apex to base on both sides but less dense in the upper lung fields. A magnifying glass reading revealed innumerable distinct sharply-outlined particles of calcium which caused the cloudy appearance and which, with magnification, resembled a snowstorm. There was no evidence of any other disease. The bones all appeared normal in calcium content and anatomic detail.

The lateral roentgenogram brought out a dense triangular homogeneous deposit of calcium in the right costophrenic area anteriorly, obviously either in or just under the pleura, with a similar but less marked deposit along the minor interlobar fissure.

CASE 10

This is the case of Mrs. DeS., aged forty-five. Through the cooperation of Dr. Walter L. Stilson, College of Medical Evangelists, Los Angeles, California, we were able to obtain a good history, a record of the physical examination, and roentgenograms of this sister's chest and also those of her 4 children. The latter were all within normal limits. The roentgenogram of Mrs. DeS., however, demonstrated the classic appearance of microlithiasis (Fig. 20).

This patient is the eldest of the four sisters, born in Italy, June 27, 1910, moved to the United States when she was ten, lived in Pennsylvania for twelve years, in New Jersey for the next sixteen years, then moved to California where she has lived for the past eight years.

She was married twenty-seven years ago. Her husband, fifty-three years old, suffers from hypertension. She has had 4 children, a female twenty-four and three males, thirty-two, seventeen, and twelve. She has had no miscarriages. Her personal habits are normal. She works in a grocery store and is on her feet most of the day. She drinks about 6–8 ounces of wine a day and smokes about half a package of cigarettes daily. Three years before her marriage she worked in a silk mill in Pennsylvania. She had a pelvic operation and repair of an umbilical hernia in 1952. Her family history is as noted in Case 7.

This patient has no present complaints and was seen only because her sisters are known to have pulmonary alveolar microlithiasis. She complains of no dyspnea either at rest or on exertion; has no chest pain, no wheezing, no palpitation and no cough. Menarche was at the age of fourteen.

Physical examination revealed a moderately obese white female, height 5 ft., 6 inches, weight 170 pounds, blood pressure 120/70, temperature 98.6°F. There was marked clubbing of the fingers with double curvature of the nails.

Chest examination revealed pendulous moderately atrophic breasts with no masses. The heart was not enlarged to percussion or on

roentgenographic study. The lungs showed dullness at the bases. Vocal fremitus was normal. Respiratory movements were symmetrical. Fine dry rales, most marked at the peak of inspiration, were present bilaterally in both bases posteriorly and anteriorly to the midlung fields. The rest of the physical examination was noncontributory.

Her roentgenogram dated July 12, 1955 (Fig. 20) revealed the heart shadow to be almost completely obscured and the entire lung fields filled with miliary particles of calcific density extending from the apices to the bases. The diaphragm leaves were completely obscured and there was minimal pleural reaction at the bases, more marked on the right side. Changes at the bases showed somewhat increased size of the nodulation with some of the nodules measuring up to 1 cm. in diameter. There was a dense ring of calcium apparently deposited on the aortic arch, with other coalescent deposits in or just under the basal pleura and the interlobar pleura. The bony structures visualized were within normal limits and the thorax showed a normal development.

CASE II*

Elijah A. is a colored male aged thirty-one. (The roentgenograms, history, and histologic slide of the pulmonary biopsy were all sent to us by Dr. Paul Bishop, Pennsylvania Hospital, Philadelphia, Pennsylvania, with permission to include the details in our report.)

This colored laborer was admitted to the Pennsylvania Hospital in October, 1955 following a sudden onset of right abdominal pain, vomiting, weakness and anorexia. Chest examination gave no positive findings other than scattered rales. The patient was febrile. Chest roentgenograms revealed a remarkable bilateral diffuse, apparently confluent, clouding of the lungs of unknown character.

He gave a history of working in a brick-moulding factory for eighteen months beginning in 1940, inhaling the dust for six or seven days a week. He had been refused for Army Service in 1943 because of abnormal chest roentgenograms. There were several episodes of pneumonitis responding quickly to penicillin during 1947, 1950 and 1952. He had been followed since 1952 by the Philadelphia Tuberculosis Center being considered as having moderately active bilateral pulmonary tuberculosis. Three months before admission he had been fluoroscoped at Temple University Hospital with an alleged result of negative upper gastrointestinal studies.

A review of all other anatomic systems gave negative results. There was no family history of tuberculosis. Physical findings in repeated examinations of the heart and lungs were consistently negative. He admitted no respiratory embarrassment except slight exertional dyspnea after climbing one or two flights of stairs.

He is presently employed in the stockroom of a large drug company and is working regularly without disability.

Chest roentgenograms were obtained of his mother, a cousin and 3 of his children (all 3 under nine years of age) which were all within normal ranges.

The diagnosis of pulmonary alveolar microlithiasis was confirmed by pulmonary biopsy (Fig. 22). The roentgenograms of his chest, dated October 19, 1955 (overexposed Bucky roentgenogram reproduced in Figure 21), revealed a perfect snowstorn pattern, with innumerable lesions, both fine and coarse, scattered uniformly throughout all lobes of both lungs. The lesions were all of calcific density. They were more numerous at the bases medially, less numerous in the apices and in the extreme costophrenic angles laterally. Some of the coarser lesions suggested a coalescence of many smaller ones. There were coarse dense lines of calcium deposits on the dome of each leaf of the diaphragm and along the minor interlobar pleura on the right. Finer lines of calcium outlined the pleural surfaces along the chest walls laterally and in the apices. There were emphysematous blebs in the apices. The heart was fairly well outlined and appeared normal in size and contour. The diaphragm was normal in position and contour. The pulmonary arteries could not be identified with certainty. There were no hilar or mediastinal masses. All of the visualized bones appeared normal in detail and calcium content. The trachea was normal.

Roentgenograms of the abdomen were made at our request and revealed no evidence of urinary calculi or abnormal calcium deposit.

The pulmonary biopsy revealed the classical laminated translucent concretions filling most of the alveoli, with a good deal of fibrosis and cellular infiltration of the interstitial tissue. There were multinucleated giant cells close to some of the calculi, and in places actual bony

* This case will probably be reported in detail by other authors in the *American Review of Tuberculosis*.

lamellae could be seen. The over-all appearance was considered typical of pulmonary alveolar microlithiasis, but with more tissue reaction than in many of the other cases.

CASE 12

Cyril P. is the brother of the patient reported as Case 2. His roentgenograms and personal history were sent to us by Dr. Perry Macgregor Knox of Moncton, New Brunswick, with permission to include them in this report.

This young man of English descent, aged nineteen in 1944, was also found by roentgen examination to have a diffuse pulmonary condition when he volunteered for service with the Canadian Armed Forces. In spite of the fact that he was apparently well and healthy as evidenced by physical examination, he was rejected. Since then he has been working regularly and has had no pulmonary disability.

His chest roentgenogram, dated October 27, 1944 (Fig. 23), revealed a diffuse mottling throughout both lungs, definitely coarser and less sand-like in appearance than that of his older brother (Case 2). Such an appearance could be due to any of the usual miliary diseases or to sarcoidosis or berylliosis, except that fine grains of calcific density were seen scattered among the larger nodules. These nodules averaged 1 to 3 mm. in size and seemed to alternate with surrounding or intervening clear areas resulting in the appearance of a coarse sponge, which usually means fibrosis and lobular emphysema. There were small but definite emphysematous blebs in each apex. Unfortunately, the roentgenogram was made with "soft" (low voltage) technique and a comparatively broad-focus tube so that details were unclear and the accurate estimation of the amount and distribution of calcific deposits was impossible. We awaited with eagerness a re-examination with overexposed Bucky roentgenogram for comparison. The cardiac outline was fairly well seen and appeared normal in size and contour. The diaphragm leaves were normal in position and contour. There seemed to be a fine line of calcium deposited on the medial half of each diaphragm leaf, probably in the pleura or subpleural tissue. The hilar vessels were indistinct but did not appear enlarged or engorged, and there was no evidence of hilar or mediastinal lymph adenopathy. The upper mediastinal borders were indistinct and the aortic knob was obscured. The trachea appeared normal. The clavicles and ribs appeared normal in density and in anatomic detail.

Comment. We could not from this single chest roentgenogram be certain that this patient had the same disease, microlithiasis, as his brother, but it seemed highly probable. All of the roentgenograms of the other patients appeared quite characteristic, even pathognomonic, but this one was in the "suspect" or "doubtful" class until further chest roentgenograms were received from Dr. E. Grenier, of Gaspé, Quebec. These roentgenograms, dated December 2, 1955 (Fig. 24) leave no doubt as to the diagnosis. They are technically of good quality with enough penetration to bring out the typical fine sand-like spots of calcific density practically overwhelming both lungs. There are still numerous larger nodules and some of the sponge-like appearance, but no other changes. Because of the marked difference in technical quality, it is impossible to say whether the condition has worsened in the eleven year interval. In general, the amount, character, and distribution of the densities appear to be about the same as at the previous examination eleven years earlier. There has certainly been no improvement or lessening of the involvement, but on the other hand there has been no definite worsening. The patient remains free of symptoms and continues his regular work.

CASE 13

The paper-mounted thin section of one lung illustrated in Figure 25 was sent to us by Dr. J. Gough, Cardiff, Wales, his case number 12,795–52, along with a similar section of Sharp and Danino's patient noted above and illustrated in Figures 14 and 15. We took roentgenograms of both specimens and this one is illustrated in Figure 25.

Many of the little grains of the sand-like material have fallen out of the lower part of the section during the process of mounting, but they are present to an innumerable degree in the upper lobe. Several of these particles have been removed under a dissecting microscope and have been studied for their crystal structure and their chemical composition.

This young woman of twenty-eight years suffered from shortness of breath for eighteen months before her death. Her past history revealed diphtheria as a child, pneumonia at the age of two and a second attack of pneumonia later, age not definite.

She was admitted to the hospital at the age of twenty-six because of shortness of breath. There was a questionable history of pneumonia six weeks earlier. She had obvious cardiac failure and was also thought to have pulmonary hemosiderosis. Re-admitted in March, 1952, with congestive heart failure, she died four days later. The cause of her death was considered to be cor pulmonale.

Autopsy revealed microlithiasis alveolaris pulmonum, which was considered to be the cause of her cor pulmonale.

The roentgenogram of a thin paper-mounted section of the lung (Fig. 25) showed numerous very small discrete dense particles scattered uniformly and diffusely through the upper lobe. The appearance was identical with that noted in a similar lung section as shown in Figures 14 and 15.

When the film was studied through a hand lens or reading glass, one saw the individual small particles more clearly. They were round or oval for the most part, sharply outlined and distinct from each other with no evidence of coalescence into larger nodules or masses. No dense conglomerate areas could be seen. The pleural surfaces were sharp and distinct, with increased numbers of the calcium granules in the subpleural zone. The major interlobar fissure was clear and distinct. The irregular branching clear areas in the upper lobe were due to empty vascular spaces, particularly large pulmonary veins.

CASE 14

This unmarried Spanish female, T.A., aged forty-six and sister of Case 3, had the usual childhood diseases, also typhoid fever in 1931, and acute appendicitis in 1952. She is subject to frequent attacks of migraine headaches.

Physical examination was completely normal, revealing the patient to be in excellent condition.

Laboratory Data: Urine: Specific gravity 1.010; pH 5.5; no sugar or albumin; urate crystals 2+ in sediment. Blood: Cholesterol 150 mg. per cent; nonprotein nitrogen 28.6 mg. per cent; red cell count 5,300,000; Hb. 14.5 gm. (100 per cent); hematocrit 50 per cent; white cell count and differential normal; fasting sugar 90 mg. per cent; Ca 4.8 mg. per cent (normal—4.2–5.1); sedimentation rate 30 mm. in one hour.

Roentgenograms of her abdomen revealed no evidence of urinary calculi or other abnormal calcification.

Three other sisters and 1 brother have not yet been examined. One of them is said to have hypertension but the others seem to be in good health.

The roentgenogram of this patient's chest (Fig. 26) revealed a very diffuse and finely mottled density throughout both lungs from apices to bases, most marked in the lower medial portion of each lung. The density in these areas was so great that the cardiac outlines and diaphragm were completely obscured. Dense calcified lungs appearing almost solid could be seen through the upper abdominal shadow, with a clear dark zone 2 cm. in diameter in the midline indicating the mediastinal space free of calcium. The normal vascular tree in the lungs was completely obscured. The aortic knob was indistinct. Both upper lobes showed a fine reticulated pattern between the individual calcific granules. The bones retained their normal density and normal anatomic detail. The appearance was considered to be characteristic of an advanced stage of pulmonary alveolar microlithiasis.

CASE 15

The patient, Mrs. Elsie W., is a married woman, aged fifty-two, who has a certain antagonism toward doctors because one of them diagnosed her as having pulmonary tuberculosis in the early 1940's and put her to bed. The diagnosis was based upon roentgenographic evidence, but the 1942 films cannot be found. The present diagnosis originated from a chest survey film with follow-up made in Dr. Waterman's office.

Mrs. W. had been working actively as a secretary and had little or no disability. Pulmonary function studies revealed definite reduction in vital capacity (55 per cent of estimated normal) and maximum breathing capacity (60 per cent of estimated normal) but her walking index was only off by 12 per cent, and she showed relatively little dyspnea on climbing one flight of stairs. Her laboratory studies revealed normal values for blood: white blood

cell count 8,900; neutrophils 56 per cent; lymphocytes 43 per cent; monocytes 1 per cent; hematocrit 38 per cent; Hb. 78; red cell count 4,290,000. The urine on two separate examinations showed a trace of albumin, no sugar, specific gravity 1.025, a few epithelial and pus cells and a few granular casts.

Pulmonary biopsy was performed on May 11, 1956 from the anterior-inferior edge of the right middle lobe. The entire lung on the right side, as far as it could be inspected and palpated through the small incision, was uniformly involved and was firm and gritty to palpation. There were no adhesions and the interlobar fissures were free. The parietal pleura was normal and the visceral pleura also appeared normal.

The biopsy (Fig. 28) confirmed the diagnosis of pulmonary alveolar microlithiasis. Dr. Gustave Dammin's report was: "Gross Description: Specimen consists of a pre-fixed piece of lung which is prismatic in shape and is 1.5×2×0.75 in greatest dimension. Two pleural surfaces are present and both appear unremarkable. The lung parenchyma itself is light tan in color and relatively airless in consistency. Numerous extremely small refractile bodies are scattered through the parenchyma. The parenchyma cuts with a definitely gritty sensation. Microscopic Examination: (3H and E, 2 Elastic Tissue, 2 von Kossa). Each alveolar space contains a concentrically laminated, dense round body which almost completely fills it. In the partially decalcified specimen, many of these bodies still retain considerable amounts of basophilia characteristic of calcification. The alveolar walls are not remarkable except for some fragmentation of their elastic fibers seen on special stains. The blood vessels and bronchi are not remarkable. No cellular infiltration or exudation is present. Diagnosis: 360–923 Lung —microlithiasis."

The roentgenogram (Fig. 27) demonstrated lungs so dense and so heavily calcified that very little of the normal lung structure could be identified. The lower half of each lung seemed to be completely solid and airless. The cardiac outline and the diaphragm could not be identified. The upper lobes evidently contained some air, but the calcium deposits were so heavy that the lungs seemed to be completely rigid, practically petrified. There was a clear space on each side, above the calcified apex of the lung and below the upper ribs, not a pneumothorax, but probably filled by fat or other soft tissue. A clear calcium-free mediastinal zone, about 2 cm. in width, could be seen up to the level of the carina. The ribs, spine and shoulder girdles appeared normal in density and structure, with no deformities. The upper abdomen was included on the overpenetrated chest roentgenogram and no renal calculi were visible.*

Comment. These are the most densely involved lungs in our series of cases, all the more remarkable by contrast with the paucity of symptoms.

CASE 16

This young man, A.C.M.R., aged thirty-five in 1956, was first found to have an unusual pulmonary condition in 1942 in London, England. This was demonstrated on a 35 mm. photofluorogram and confirmed by large films on October 3, 1942. The condition was reported as "bronchiolitis obliterans." Subsequent roentgenograms were taken at the Brompton Chest Hospital in 1950 and in Tooting in 1951, both said to show no change as compared with the 1942 roetgenogram. The recent (1955) rediscovery of the pulmonary condition was through another routine chest roentgenogram taken as part of an examination for life insurance. The patient in 1942 had no history of any pulmonary disease or disability, and after five weeks of observation and tests was returned to full duty with the British Air Force. He spent three

* Subsequent chest roentgenograms taken on deep inspiration and forced expiration demonstrated conclusively that each lung can and does expand both transversely and longitudinally. By careful measurement the calcified lungs increased in length 1.2 cm. on the right and 0.9 cm. on the left. Simultaneously each lung increased 1.2 cm. in width at the junction of middle and lower thirds on each side, where the concentration of calcium particles appeared greatest. In addition, careful comparison of the two roentgenograms revealed an appreciable difference in the air content in both upper and lower lobes, with more radiability of the lower lobes, particularly, on inspiration, while they appeared practically airless on expiration. Furthermore, Bucky roentgenograms now reveal calcified lymph nodes just below the carina forming a small mass 1.5×2.5 cm. in size. This is the only case in our series where we have been able to identify calcium deposits in lymph nodes.

If these minute calculi should by chance lose their covering of alveolar wall and septa and should rub together on breathing, some alert physician might then hear a peculiar sound which, when once recognized and described, might be one of the two possible methods of diagnosisng this extraordinary disease aside from roentgen examination. However, it would be confusing rather than helpful to call this theoretical sound "respiratory calculation."

The other possible method would be to find and identify the microliths in the patients' sputum as Lindig[9] has suggested. They probably raise such calculi from time to time, but only 1 patient so far is recorded as having mentioned it.

years with the Air Force in the Middle East, and came to Canada in 1951.

His family history revealed that his father died at the age of forty-two from "pleurisy and congestion." He was sick about four months before he died. No chest roentgenograms were taken. His mother is alive and well. There was some question about her chest roentgenograms at the time of her entry into Canada, but she was subsequently admitted. These chest films were reviewed by Dr. Sieniewicz and no evidence of microlithiasis was found. One brother died at five years of age of meningitis.

The patient has no symptoms at present and physical examination was completely negative. He was physically in good condition, had no dyspnea or cyanosis, and had observed no difference in his exercise tolerance. He plays badmington twice a week with no difficulty. There was no clubbing of the fingers. Inspection, palpation, percussion and auscultation of the chest were all within normal limits.

Attempts were made to obtain pulmonary function studies and laboratory tests but the patient did not accept the suggestion.

A letter from Dr. Clifford Hoyle of London, who saw this patient in 1950, adds the information that the original 1942 roentgenograms were "thin and of poor quality," but that they showed very fine mottling of both lungs without hilar lymph node enlargement or cardiac enlargement. His more recent chest films were destroyed in the disastrous fire of 1950. Dr. Hoyle adds that he could see no definite change in the pulmonary involvement between 1942 and 1950. Roentgenograms of his hands and knees in 1950 were considered to be normal. He gave no history of occupational exposure nor of any use of oily sprays or nasal drops. His physical examination was completely normal, a blood cell count was normal, but his Mantoux test was positive at 1 T.U. He remained under intermittent observation until December, 1951, when he left for Canada. No pulmonary function tests were made.

His chest roentgenograms dated October 19, 1955 (Fig. 29) revealed the strikingly diffuse fine mottling of calcific density quite similar in distribution and in detail to the preceding cases. Overexposed Bucky roentgenograms brought out the contrast between soft tissues and the opaque calcific deposits, but they magnified and distorted the individual lesions. Exposures were made in inspiration and expiration which demonstrated considerable change in the size and shape of the lungs indicating good elasticity. The density in the lungs obscured the outlines of the heart and the diaphragm on the non-Bucky roentgenograms. The bones of the thorax were normal in calcium content and structural detail.

Comment. This healthy young man has had this rare pulmonary condition for at least fourteen years and yet suffers no disability from it.

CASE 17

Arthur M. was a thirty-nine year old Armenian tailor who came to the Massachusetts General Hospital Out Patient Department in April, 1931, complaining of cough of two years' duration, gradual in onset. He had no chest pain or hemoptysis. The cough produced one to two teaspoonfulls of white sputum and was worse at night. There were occasional night sweats. During the past winter he had lost 10 pounds in weight, had dyspnea on exertion and fatigued easily. Six years ago his attention was called to a change in his finger tips.

On physical examination his breathing seemed to be chiefly diaphragmatic. The right supraclavicular fossa appeared retracted. There was increased resonance anteriorly, diminished posteriorly, over both apices. Coarse dry rales were heard throughout both lungs posteriorly and over the right anterior chest.

Laboratory Data: Sputum was negative for tubercle bacilli on three separate days; cultures for fungi and yeasts produced no pathogenic organisms. Clinical laboratory tests revealed: nonprotein nitrogen 36 mg. per cent; serum calcium 11.6 mg. per cent; phosphorus 4.1 mg. per cent; CO_2 combining power 64.2 vol. per cent; O_2 capacity 22.52; vital capacity 2.25–2.50 l.; basal metabolic rate +7; repeat serum calcium 11.7 mg. per cent; phosphorus 3.78 mg. per cent. Tuberculin test was performed but not recorded.

Roentgen examinations were reported by Dr. George W. Holmes as follows:

"April 13, 1931: Chest—no normal lung field visible on either side of chest. At extreme apex on right there is a large rounded bright area with dense margin which probably represents cavity. Trachea drawn to this side. Throughout both lung fields there is fine, mottled density. Shadows are about the density of

bone and increase somewhat toward the bases, obliterating outlines of borders of heart and of diaphragm. Appearance suggests extreme calcification of both lungs."

"April 23, 1931: Appearance of lungs suggests emphysema and calcification throughout both lungs with cavity in apex. There is probably tuberculosis present but greater part of picture is due to calcinosis."

"May 19, 1931: The skull and long bones are negative. Abdomen: The upper portion of the urinary tract is obscured by the dense shadows in the lung fields. There are no shadows suggesting stones."

On May 29, 1931 the patient and his roentgenograms were presented at Grand Rounds. The conclusions were that his condition was due to a peculiar type of pulmonary tuberculosis and that sanatorium care was justified. This was refused by the patient.

A follow-up in 1956 revealed that this patient, apparently frightened by the diagnosis of pulmonary tuberculosis, left Boston for his original home in Egypt on June 24, 1931 and has not been heard from since.

Reviewing his chest roentgenogram (Fig. 30) in the light of our present knowledge, we see the characteristic appearance of a well advanced case of pulmonary microlithiasis. The "bright area" in the right apex which suggested a cavity is, in all probability, an emphysematous bleb similar to those seen in Case 1 roentgenographically (Fig. 3) and confirmed at autopsy. We seriously doubt if he ever had pulmonary tuberculosis. The cryptic note about the change in his finger tips probably indicates clubbed fingers, which in turn could indicate a fairly marked degree of pulmonary insufficiency. The pulmonary involvement, as judged by his roentgenogram, is also fairly marked, with airlessness in some areas, complete obscuration of the heart shadow and diaphragm, and emphysematous blebs in both apices, but still much less massive than in Case 15, which was still asymptomatic.

CASE 18

All clinical records of this patient have been lost or destroyed and the history is largely reconstructed from memory.

A tall, thin, female school teacher about forty-five years old was referred for chest roentgenograms on March 28, 1932 because of respiratory distress interpreted as asthma. The chest roentgenograms were so unusual that they were shown to most of the leading roentgenologists of the Philadelphia area, but no one was able or willing to make a diagnosis. It was agreed by all that the fine diffuse mottling of both lungs was of calcium density, but no one knew what it was, nor could anyone remember having seen a similar case. Copies of the roentgenograms were made and the originals were sent to the British Institute of Radiology in London for deposit in their film museum of unusual cases. Nothing was heard from the Institute regarding the films or a possible diagnosis.

No biopsy was performed. The patient was lost to follow-up and nothing has been heard of her since 1932.

The roentgenograms (two posteroanterior and one lateral films) present the classic appearance of pulmonary alveolar microlithiasis, now that we know what that is (Fig. 31). The fine granular mottling is uniformly distributed throughout both lungs from apex to base, of calcific density, most marked in the right base where the heart border and diaphragm are almost obscured. There is a suggestion of increased density along the branches of the pulmonary vascular tree. No consolidation, cavitation, atelectasis or emphysema can be seen. Using a hand lens over the apical areas, the individual fine calcific granules can be detected. The diaphragm is low but of normal curvature. The heart is enlarged downward and to the left. The aortic knob is indistinct. The spine shows a slight double scoliosis, but the bones all appear normal in density and structure.

Several men, learning of her occupation as school teacher and the daily use of chalk for twenty years, suggested that inhaled dust from chalk might be the answer.

CASE 19

J.O. is a single female of Mexican parentage aged twenty-six. She was first seen in June, 1953, with a complaint of cough and pain in both shoulders. Examination at that time revealed a normal appearing young woman weighing 99 pounds, with a temperature of 99° F. and a pulse rate of 96. Her sedimentation rate was 37 mm. in 1 hour. Her sputum was negative for acid-fast bacilli. Roentgenograms of her chest were said to reveal bilateral pulmonary calcification. Admission to the Texas

State Tuberculosis Sanatorium was applied for and in the meantime the patient was placed on bed rest and symptomatic therapy. By August, 1953 (2 months) she had gained 8 pounds.

Before hospital admission could be obtained, the patient joined a cotton-picking expedition to Arizona, but because of weakness, cough, and shortness of breath, she consulted a physician (Dr. E. W. W.) of Eloy, Arizona. A diagnosis of miliary tuberculosis was made, presumably from the roentgenographic appearance alone, and the patient was placed on streptomycin injections twice a week (dosage not mentioned) and so continued from October 10, 1953 to January 6, 1954.

On February 1, 1954 the patient returned to Taft, Texas, again under the care of her original physician who continued the streptomycin therapy and added isoniazid, 100 mg. twice each day. On March 22, 1954 she was admitted to the East Texas Tuberculosis Hospital, Tyler, Texas, where she remained until November 10, 1954 (7 months, 19 days). Physical examination revealed a temperature of 99° F., weight 110 pounds, blood pressure of 120/90 and impaired percussion in both bases with reduction of auditory phenomena. No rales were heard. Routine laboratory data were essentially normal. Repeated sputum concentrates as well as gastric and bronchial washings were negative for acid fast bacilli. Roentgenograms of the chest "revealed stringy disease bilaterally which appeared to follow a definite lymphhematogenous pattern. The transverse fissure was thickened and visualized. The mediastinal silhouette as well as the hemidiaphragm were obscured by a homogenic calcific density."

A purified protein derivative (PPD) test was positive. The patient was continued on antibiotic therapy. Cultures for fungi were negative. Bronchoscopy (April 13, 1954) proved a normal tracheobronchial tree and two collected specimens were negative for fungi and tubercle bacilli. Skin tests with coccidioidin and histoplasmin were positive (degree not stated). Exploratory thoracotomy (September 25, 1954) by Dr. Howard Barkley revealed the lung field free of adhesions except for a fairly long fibrinous band over the upper pole. The apex of the left lung was gritty and granular with thickened and rather edematous lung tissue. There was no pleural fluid. The lingula was clamped and a good-sized piece of lung tissue was removed. On section the lung tissue was gritty. The heart appeared normal during exploration.

Studies of the biopsy material by Dr. Mullowney revealed "circular, somewhat granular bodies of varying size, many of which have a laminated appearance. I have never seen this type of pulmonary lesion before and can find nothing comparable to it in text-books . . ." She was discharged with a diagnosis of "metastatic calcinosis."

The patient then spent two months in Arizona and returned to Taft, Texas, where she has resided to date, coming to Corpus Christi, Texas for study on January 14, 1956.

The past history except as stated in the present illness was entirely negative. The family history revealed a mother, a father, 2 brothers, and 4 sisters to be living and well; all with negative chest roentgenographic studies. One brother died at six months of age from an unknown cause. The patient was single, having regular normal menstrual periods without intermenstrual discharge.

Physical Findings: Weight 106 pounds; height 61 inches; temperature 99° F; pulse 82 per minute; respiration 20 per minute; blood pressure, right arm 114/80, left arm 110/80. There was no edema, icterus, dyspnea, cough, paresis, or cyanosis while examination was performed. Except for mild facial acne the skin was normal. The head and neck were negative except for mud colored sclerae. The fundi were normal. There was no lymphadenopathy. The thyroid was normal to palpation. There was no engorgement of the neck veins. Expansion of the chest was markedly curtailed with an expiration circumference of 30½ inches and an inspiration circumference measuring 31 inches. The breasts were normal. Percussion note was impaired over the lower lung fields but fairly good breath sounds were heard. No rales or friction rub were audible. The point of maximal impulse was thought to be within the left midclavicular line. The heart rate and rhythm were normal. No murmurs were audible. The abdomen, extremities, and reflexes were within normal limits. Muscle, tendon, and joint sense, discriminatory and vibratory sense were normal. Laboratory Data: Red blood cell count 4,380,000; hemoglobin 12.6 gm. (86 per cent); white blood cell count 8,400; polymorphonuclears 75 per cent (stabs 4 per cent); lymphocytes 21 per cent; monocytes 3 per cent;

and eosinophils 1 per cent. The urine revealed a pH of 7.0; specific gravity 1.010; negative tests for sugar and albumin; and a negative microscopic examination of the sediment. The blood sugar was 82 mg. per cent; nonprotein nitrogen 29.5 mg. per cent; cholesterol 211 mg. per cent; sedimentation rate 10 mm. in 1 hour corrected; hematocrit 42 per cent. The alkaline phosphatase was 2 King-Armstrong units. The blood calcium run on January 14, 1956 and January 18, 1956 was 11.9 mg. per cent and 11.6 mg. per cent, respectively; blood phosphorus 2.00 mg. per cent; Kline precipitation test negative; blood chlorides 510 mg. per cent; total proteins 7.6 gm. with albumin of 4.32 gm. and globulin of 3.28 gm. and an albumin globulin ratio of 1.3. Examination for lupus erythematous cells was negative. Cephalin flocculation test was 3+. The protein bound iodine measured 6.0 μg. per cent. Blood culture was negative. Sputum examination with Pappenheim's stain and acid fast bacilli concentration stains and cultures for acid fast bacilli, fungi, and ordinary microorganisms were negative. Guinea pig inoculation was reported negative with the animals autopsied six weeks after inoculation. Intradermal tests with histoplasmin 1:100 dilution gave a red blush with a diameter of 0.5 cm., while with blastomycin 1:100 dilution were entirely negative. Wheal formation was absent in all tests. Vital capacity on three occasions ranged between 32 and 52 per cent of the predicted normal.

The electrocardiogram was interpreted as showing only sinus tachycardia with a rate of 107 per minute. Roentgenographic examination of the chest revealed a diffuse bilaterally symmetric, extremely dense, finely granular mottling. The bases were more dense than the apical regions. This was thought to be due to the increased anteroposterior diameter of the chest rather than the actual increased density. All segments of the lung were involved. The minor interlobar fissure on the right was thickened with the possibility of calcific pleuritis here as well as in the upper portion of the diaphragmatic pleura on the left, where there was a rim of calcium paralleling the upper contour of the diaphragm. The findings were consistent with those described in pulmonary alveolar microlithiasis. (J. Gardner, M.D., Radiologist).

Lateral stereoscopic roentgenograms of the skull, an anteroposterior roentgenogram of the abdomen, and anteroposterior roentgenograms of the hands revealed normal bone densities, without evidence of abnormal calcification. The kidneys appeared normal without evidence of stones.

The microscopic slides of the lung biopsy material, made at the East Texas Tuberculosis Hospital and kindly loaned by Dr. J. P. Mullowney, were examined by us (Fig. 33) and reported by Dr. John F. Pilcher, Pathologist as follows: "The slides show lung tissue with a large majority of the alveoli containing spherical bodies which are apparently calcified. These rounded bodies are finely laminated concentrically and in some instances fractured irregularly. The alveolar walls show little change from normal and are of normal thickness. There is very little, if any, inflammatory change present in the lung tissue. This seems to be a typical example of pulmonary alveolar microlithiasis."

The patient is now on restricted activity with only symptomatic therapy from time to time. She fares reasonably well and has respiratory symptoms only with overexertion.

A re-study of her chest roentgenograms (Fig. 32) confirmed the presence of innumerable coarse calcific densities scattered uniformly throughout both lungs. The lesions appeared larger than those in other cases (averaging 2 mm. in diameter) with a definite spongy and reticular pattern, suggesting lobular emphysema alternating with a network of airless tissues. The appearance was unusual in detail, but the total picture conformed to the patterns previously described. There were emphysematous areas in each apex, and retraction of each apex from the bony thorax, the intervening spaces presumably being filled with fat, not by pneumothorax. There were accentuated linear collections of calcospherites along the minor pleural fissure on the right and over the dome of the left diaphragm, measuring 2 mm. in width. The cardiac outlines were completely obscured, even in Bucky roentgenograms, and the diaphragm could be seen only in the lateral view. It appeared normal in position and curvature. No calcium deposits could be seen in the mediastinum or in the hilar lymph nodes. The bone detail and calcium content were normal.

A roentgenogram of the abdomen revealed no enlargement of the liver or spleen. The kidneys were well outlined, normal in size and shape with no evidence of urinary calculi. No

abnormal deposits of calcium could be seen anywhere except in the lungs.

CASE 20

This patient, G. P., a white male, was sixty-six years of age when he died in 1953 in the Winnipeg General Hospital. Autopsy was obtained and the diagnosis of pulmonary alveolar microlithiasis established. The patient had been under observation since 1928 when he first noticed shortness of breath on exertion. He was admitted to a sanatorium but the diagnosis of pulmonary tuberculosis (presumably from roentgenograms) was not confirmed. His dyspnea gradually became worse, requiring admission to the hospital for treatment of heart failure. His final admission was on September 11, 1953, when he presented severe dyspnea and cyanosis and died a few hours later.

Past history revealed no previous illnesses except as noted above. His family history was noncontributory. He had worked most of his life on a farm and had no exposure to silica or any other dusts or toxins as far as could be determined.

On physical examination hypotension was found, blood pressure 70/30, with a pulse of 60, completely irregular. Temperature was 96.4° F. There were cyanosis of face and hands, and pitting peripheral edema; the liver was palpable three fingers below the costal margin and there were rales throughout the right chest. In spite of administration of oxygen and penicillin he expired.

Laboratory investigation during a previous admission (October, 1952) revealed that tests for tuberculosis, torulosis, histoplasmosis and blastomycosis were all negative. Blood urea nitrogen was 23 mg. per cent. Prothrombin time, blood examination and sedimentation rate were normal. Tests of the urine were negative; an electrocardiogram was interpreted as showing chronic right ventricular strain and partial atrioventricular block. Roentgenograms in 1949 and in 1952 were interpreted as "fine mottled type of increased density . . . completely obscuring lower two thirds of both lung fields . . . suggests possible pneumoconiosis or fungus type of infection." There was no change in appearance from 1949 to 1952.

The autopsy, by Dr. D. W. Penner, including the brain, revealed nothing significant except in the chest. The brain, pituitary gland, mediastinal lymph nodes, thyroid, spleen, kidneys, liver, pancreas, adrenals, testes and prostate were normal except for congestion. The gallbladder contained 5 calculi. The gastrointestinal tract appeared normal throughout.

The heart weight was 380 gm. and there was hypertrophy of the right auricle and ventricle. No abnormality of the valves was mentioned.

The right lung weighed 3,640 gm. and the left, 2,550 gm. There were numerous pleural adhesions. Cut sections of the two lungs were identical, reddish-brown in color, grossly emphysematous, with a small cystic honey-combed appearance. Most spaces were less than 1 mm. in diameter but up to 5 mm. in the apices. Scattered throughout the parenchyma were numerous glistening sand-like bodies of fairly uniform size, mostly less than 0.5 cm. They were pale, light yellow in color and felt like fine sandpaper on the cut surface.

Microscopic examination of the lungs revealed a "diffuse calcinosis." There was some emphysema, most marked in the apex and some patchy interstitial fibrosis, not marked. Most of the alveoli contained laminated calcareous masses, many of which practically filled the alveolus.

Roentgenograms dated March 22 and 23, 1949 and June 20, 1952 (Fig. 34), all overexposed Bucky films, were made available for study. They all presented the classic appearance of an advanced case of pulmonary alveolar microlithiasis, with no appreciable change between the two sets of films. In addition to the innumerable fine granular calcific deposits scattered universally throughout both lungs, there were emphysematous areas in both apices, larger on the left, and at the basal periphery of the lungs, more on the right. The cardiac outlines were completely obscured and the outlines of the diaphragm leaves were only faintly visible on one film but apparently normal in position and contour. The clear (uncalcified) zone in the mediastinum was distinct and there were no calcium deposits visible in cervical or mediastinal lymph nodes, spleen or liver. The bones appeared normal in detail and density.

Comment. At the present time it is impossible to state the duration of this man's disease, but it probably dates at least from 1928 when he first had symptoms until his

death in 1953, a period of twenty-five years. If we assume the usual preceding asymptomatic or latent period, it might easily be twice this figure.

We are trying to find some of his earlier records and will also try to investigate his family for other cases of this singular disease.*

CASE 21

The chest roentgenograms, clinical history and a histologic section of the pulmonary biopsy of Case 21 were sent to us by Dr. J. Stauffer Lehman of Philadelphia with the approval of the patient's medical consultant, Dr. Peter Galamaga, of Philadelphia, Pennsylvania, and permission to include the details in our report. The patient, M. G., a fifty-two year old female, was admitted to the Memorial Hospital in West Chester, Pennsylvania on June 14, 1956, with complaints of recent upper respiratory infection, slight fever and increased exertional dyspnea and fatigue.

The family history revealed that the patient's mother died of some form of pulmonary disease, undiagnosed, with no record of roentgen examination. The patient's father also died from an unknown cause. She had no brothers or sisters and has had no children.

Her past medical history was essentially negative except that she first noted exertional dyspnea at the age of fourteen while walking on level ground for three or four blocks. This continued until the age of twenty-one but the patient claims it was not disabling. She was free from exertional dyspnea from age twenty-one to fifty-one and carried on normal activity during that time. For the past year she has been prone to upper respiratory infections which have been difficult to clear up. There has been no hemoptysis and no exposure to harmful dusts or gasses as far as known. Her chief employment has been that of baby-sitter.

The only previous illness of any consequence was proved Rocky Mountain spotted fever in 1952. This resulted in her first hospital admission during which she had routine chest roentgenograms taken. These revealed extensive pulmonary changes, later found to be pulmonary microlithiasis.

On physical examination the only abnormal findings were slight clubbing of fingers and toes, an increased pulmonary second sound and diminished breath sound with rales in both lower lobes posteriorly. The rales did not clear up on coughing.

An electrocardiogram revealed only right axis deviation. All remaining laboratory tests were within normal limits. No pulmonary function tests were done.

Dr. Robert Glover performed a lung biopsy. An uneventful postoperative course followed. The tissue removed was described by Dr. Joseph Imbriglia of Hahnemann Hospital, Philadelphia as "a triangular piece of tissue, measuring 3.0×2.5×1.0 cm. The pleura is smooth and shiny. Cut section is made with some resistance and is rubbery and granular in consistency. Microscopic examination reveals pulmonary parenchyma characterized by the presence of calcific depositions within many of the alveoli. The depositions are circumscribed, laminated, ovoid masses which appear to occlude the alveoli. The masses take on a bluish-pink color with H. and E. stain. The alveoli themselves are usually dilated, due to the presence of these masses. The alveolar walls show varying degrees of fibrosis. There is monocytic proliferation with occasional giant cell formation" (Fig. 36).

Roentgenograms of various dates from June 12, 1952 to June 24, 1956, with various techniques were made available for study. All of the films showed the same characteristic appearance of fine diffuse granular deposits of calcific material throughout both lungs from apex to base. With ordinary exposure technique only the apices were penetrable. Even in Bucky roentgenograms (Fig. 35) the cardiac outlines and the diaphragm shadows were completely obliterated. Using a hand lens, a very fine mesh-like appearance was brought out similar to a sponge, but with tiny individual grains of sand between the holes in the sponge. There was no apparent coalescence or conglomeration of the deposits, but they were accentuated along the pleura, particularly the interlobar fissures, and in a coarse irregular manner along the branchovascular tree. There was bullous emphysema in the left apex of moderate size.

* The earliest roentgenographic report on file, dated June 25, 1929, reads "Both diaphragms and the lower half of the chest are obscured. There is a dense miliary spread throughout both lungs. Likely non-tuberculous. May be malignancy or blastomycosis." This would indicate that the condition was present in 1929 and the total *known* duration of his disease ending in his death in 1953 would therefore be twenty-four years.

At the time of going to press no report on a roentgenographic survey of his family has been received.

There was no gross distortion of pulmonary architecture, as judged by the position of the trachea, main bronchi or the clear zone outlining the mediastinum. The bones appeared to be normal in calcium content and in anatomic detail.

All of the calcified particles which were visible individually seemed to be less than 1.0 mm. in diameter, but there were several dozen larger calcified deposits in the left upper quadrant of the abdomen presumably in the spleen, which varied from 1.0 to 5.0 mm. in size. They appeared quite different from the pulmonary microliths, being smoothly rounded, larger and denser, and strongly suggested the calcified granulomas of histoplasmosis. No similar shot-like shadows could be identified in the lungs, but they could easily be present and obscured.

The anteroposterior diameter of the chest appeared increased in the lateral view.

Comment. These roentgenograms present the appearance of a far-advanced case of microlithiasis and it is considered remarkable that the patient has no more difficulty with breathing than she does. This is the first case in which calcified nodules in the spleen have been found, but they are probably incidental and may well be due to previous infection with Histoplasma capsulatum.

CASE 22

M. J. T., a white female, is now twenty-five years of age, married and has one child and is teaching school with no obvious disability. She was born July 22, 1931, in Arizona, where the family home was located six miles from a copper smelter. After seven years they moved to Colton, California, living just across the street from a large cement factory for six years and then moved to Pasadena where they now live. Mary Jo was the eldest child of three. The youngest, Timothy, also has microlithiasis but the second child has not been examined. The mother had a chest roentgenogram in 1949 which was considered to be normal.

Mary Jo was found to have the condition when her High School graduating class had minifilms of their chests made. She was sixteen years old at that time and has been followed ever since.

Her medical history was not remarkable except for chronic sinusitis which she has had since the age of eight. For it she received weekly injections of autogeneous vaccine for several years, at least through 1948 (aged seventeen). She remembers a long series of colds with an irritative cough in 1944. At this time she was thin and failed to gain weight the following year. After the discovery of her pulmonary condition in 1947, she had a thorough physical examination. The significant findings were: weight 120 pounds; height 5 ft. $6\frac{3}{4}$ inches; vital capacity 2,900 cc.; blood pressure 112/70; temperature 98° F., pulse 60. There was no evidence of clubbing of the fingers, no glandular enlargement could be found, the spleen could not be felt, and all other findings were negative including physical examination of the chest.

In 1954 she was seen again by the same physician. She had undergone infectious hepatitis with marked jaundice in October, 1952, but had no other illnesses. There was no dyspnea and only a slight occasional cough. Her blood pressure was 110/70 and physical examination of her chest again was negative.

Roentgenograms of the chest dated April 24, 1947, October 7, 1947, May 20, 1948 (Fig. 37), August 24, 1951 and July 13, 1954, were available for study. No appreciable difference in the pulmonary involvement could be seen over this period of seven years. All of the films presented the remarkable appearance of a snowstorm uniformly spread throughout both lungs. The involvement was most marked in the bases medially and least marked in the apices. The cardiac shadow could be distinctly outlined and both leaves of the diaphragm could be seen. The heart and diaphragm appeared normal. There was no gross distortion of thoracic or intrathoracic structures. The soft tissues of the neck and chest all appeared normal, the ribs and shoulder girdles were normal, and no calcification could be seen in the liver or spleen. The kidney areas were not included.

Detailed study with a reading glass of the calcified deposits in the lungs revealed innumerable small spherical calculi crowded together everywhere throughout both lungs. In addition there were coarse irregular collections of these microliths in linear distributions along pleural surfaces and along the bronchovascular tree. The latter is well demonstrated in Figure 37, in the left base where it shows through the air bubble in the stomach. A third pattern of grouped microliths is best seen in the middle and lower thirds medially, where it presents an ir-

regular interlacing web suggesting lymphatic or perivascular anatomic concentration.

CASE 23

Case 23 is the younger brother of Case 22. Timothy T. was born on October 31, 1941 in Colton, California, lived there three years and since then has lived in Pasadena. He was found to have pulmonary microlithiasis in 1949 at the age of eight years. His medical and personal histories are unremarkable. He had the usual childhood diseases as well as several episodes of otitis media in childhood. He seemed to be outwardly normal in all respects. There are no records in his case of physical examinations or laboratory tests as the family has refused further follow-ups, even when offered without charge.

The father of these children has not had a roentgenographic examination of his chest as far as we know, and the second child, a son born in 1933, has no record of chest roentgenograms.

Timothy's roentgenogram, dated July 13, 1954 (Fig. 38) when he was thirteen years old, presented the classic sandstorm appearance of pulmonary microlithiasis. With a hand lens the calculi were seen to be circular or oval, sharp in outline, distinct from each other but arranged in various patterns conforming to the local anatomy. None of the calculi seemed to be above 1.0 mm. in diameter and most of them were below this in size. The diaphragm shadow can be seen fairly well but the cardiac outlines are indistinct, probably due to the fact that this was a non-Bucky roentgenogram of rather "soft" technique. Due to this technique even the ribs appeared indistinct near the spine. The heart did not appear enlarged and the bones all presented normal density and good structural detail. No calcification could be seen in the liver or spleen. The kidney areas are not included. The epiphyses of the shoulder and wrist appeared within the normal range for a boy of thirteen.*

CASE 24

Mr. C., a white male of forty-five knew nothing of his chest condition until he applied to join the Australian Air Force during the war. Routine roentgenograms demonstrated something radically wrong with his lungs and he was rejected. He insisted that he had been perfectly well all of his life and had never had any trouble referable to his chest. Indeed he stated that he had always been remarkably free from illness. The only illness he could remember was a short febrile one when he was in the Middle East during the war necessitating bed rest for a few days. There was no history of urinary difficulty and no record of anything to suggest bilharziasis. He had been a clerk all of his life and had never worked in any of the dusty trades.

Physical examination was completely negative. He looked and felt well. His blood count was normal but no other laboratory record could be found, and he did not submit to any extensive laboratory investigation.

Two roentgenograms dated July 8, 1940 and July 16, 1942 were made available for study. Each one revealed the characteristic finely mottled sandstorm uniformly involving each lung from apex to base. The heart and diaphragm could be outlined on the second film which had been taken with twice the normal exposure. The heart was small and ptotic, otherwise normal in appearance. The vascular trunks could be recognized through the sandstorm and were normal in distribution. Small areas of emphysema could be seen in the apices and a larger area was present in the left base laterally, but there was no distortion of the other normal architecture. A few beaded and streaky areas in each apex raised the question of a possible minimal apical scarring preceding the microlithiasis. There was no cavitation demonstrable and no other calcification than that in the microliths. The reading glass again brought out the innumerable tiny sharp individual grains of sand which are so typical of this condition.

On follow-up it was learned that he died in 1947 of "congestion of the lungs" while under the care of an "irregular" physician. There was no autopsy.

REVIEW OF PREVIOUSLY REPORTED CASES

We have been able to find in the literature reports of only 20 cases of this disease which we believe fit all the criteria for inclu-

* Further investigation of the family after this paper had gone to press brought out the information that the father had several times been examined by miniature films and each one had been reported as negative.

The second child, a son, now aged twenty-three, has also had his chest roentgenographed at a Naval shipyard where he works and was reported to have no evidence of microlithiasis.

sion as "proved beyond a reasonable doubt" and 2 other cases about which there is some doubt. Most of the early cases have been reported by pathologists after autopsy confirmation, but some of the more recent reports include several which have no histologic verification, only the characteristic roentgen appearance. This is the usual course of events. A new disease or condition is discovered or identified at autopsy and thoroughly described, and then, perhaps years later, some characteristic sign or test is found by which the diagnosis can be made "beyond a reasonable doubt." Such was the case with coarctation of the aorta. For years it was a pathologic curiosity until in 1929 Railsback and Dock[53] published their article calling attention to the notching of the ribs which was found on the chest roentgenograms in nearly all cases. Then the condition became a roentgenologically diagnosed anomaly until the clinicians realized that they could anticipate the roentgenologic diagnosis by feeling for the femoral pulses and, when weak or absent, taking the blood pressure in the legs as well as the arms. At the present time coarctation of the aorta can be readily and accurately diagnosed by several different methods and, again as usual, has been found to be more common than was even suspected thirty years ago. So it is with pulmonary microlithiasis, once the characteristic roentgen appearance is recognized and understood the diagnosis can be made with a high degree of certainty if all the criteria are fulfilled. In fact, we feel that the roentgen appearance is essential to the diagnosis and can be used instead of a biopsy. For that, and other reasons which will be given below, we have not hesitated to exclude several cases which have previously been accepted as pulmonary microlithiasis and so listed in several publications. Once such an error has been perpetrated, it is commonly repeated and carried on in subsequent papers until some skeptical author reviews the entire series. Fortunately, the series in this disease is short and the cases are few, but in spite of these facts several cases have been accepted without evidence to justify their inclusion. In some even the autopsy results have been misinterpreted or classified differently by subsequent authors.

The disease or condition was first described by Harbitz[4] in 1918 and all criteria for the diagnosis were adequately fulfilled in his case. The details are summarized below. He missed the fact, however, that the calculi start *inside* the alveoli and described them as being *interalveolar* and compressing the alveoli. The next case was described by Schildknecht[17] in 1932, classic in all of its details, but described as calcified corpora amylacea rather than calculi. The amyloid reaction was negative. This was the first case in which the roentgen findings were described, although Harbitz in his 1918 articles includes a roentgenogram of a slice of the lung after autopsy, reporting a marked increase in the opacity of the specimen to the roentgen rays.

The third case was reported the following year, 1933, by Ludwig Puhr[15] and it was he who gave the name "microlithiasis alveolaris pulmonum" to the condition. Puhr thought he had discovered a new disease although he mentions Harbitz under the authors who described "calcium metastases."

Subsequent single cases were described by Mariani, *et al.* (1949),[11] Leicher (1949),[8] Lindig (1951),[9] Benard, *et al.* (1950),[2] and Sharp and Danino (1953).[18] The first to report multiple cases in one family was Mikhailov from Bulgaria, in 1954,[13] with a total of 4 cases, 3 of them in one family, *viz.*, a thirty year old female, her forty year old brother and the seventeen year old son of the brother. His interpretation, however, was that the familial cases were due either to environment or to contagion rather than heredity. Numerous cases followed in 1954 and 1955, including Manz (1 case),[10] Petrányi and Zsebök (1 case),[14] Takahashi (1 case),[19] all in 1954 and Badger, *et al.* (1 case, Case 1 in this report),[1] Sato (3 cases

in one family, all sisters, aged nineteen, ten and six,[16] Hirota (1 case),[5] and Kent, *et al.* (1 case).[6] J. Gough[3] gave additional information on Sharp and Danino's patient, and just recently Meyer, *et al.*[12] have made a second report on the patient reported by Kent, *et al.* Thus we have a total of 21 individual patients with this disease, one of them being doubtful (the case of Benard, *et al.*), the rest being proved either by autopsy, biopsy or the characteristic roentgenograms. Details are summarized below in chronologic order.

In addition to these indubitable cases, there are several cases which have been included in previous reports as belonging in this same classification. Some authors refer to Friedreich[35–37] as being the first one to describe this condition. We doubt this as Friedreich's first 2 cases are described as "corpora amylacea" in the lungs, found at autopsy, both patients dying of typhoid fever. The interstitial and intra-alveolar precipitates were of completely homogeneous character, partly in concentric layers, with "water-clear to yellowish wax-like colloidal glimmer." No mention is made of calcification or concretions in the exudates and the author's conclusions were that the condition was due to capillary extravasations. We think these cases should *not* be considered as microlithiasis.

Two other cases previously included by several authors as ones of microlithiasis are those of Jona[43] and Munk.[48] These appear to us to be classic cases of pulmonary hemosiderosis secondary to mitral stenosis, as in fact the authors themselves suggest. Jona's title of "Mitral Disease and Brown Induration of the Lungs" and Munk's title of "Disseminated Calcification in the Lung in Mitral Disease" clearly indicate the cause and the result, and we see no reason for including them with pulmonary microlithiasis. In both cases the autopsy details, histology and the roentgenograms, together with the finding of iron deposits in the pulmonary nodules, exclude microlithiasis. In both patients there were metaplastic bone formations in the lungs as well as calcium deposits around the hemosiderotic nodules, which may have led to the erroneous decisions to include them with true microlithiasis cases.

There is some doubt about the case of Benard, *et al.* based chiefly on the fact that roentgen examination (fluoroscopy only) showed nothing abnormal, and that roentgenographic examination of the lung postmortem showed no calcific micronodules. In addition, the patient was seventy-two years old and died with symptoms and signs of acute pulmonary edema. The histology, however, appears barely compatible with microlithiasis and we cannot explain the discrepancies. We would include the case with reservations and speculate that this could be an acute process ending up with similar histologic appearances but not the same disease exemplified by long duration of an asymptomatic phase and characteristic roentgenograms.

A similar situation exists in the case described by Klemm[7] except that no biopsy or autopsy material was available, but which might have avoided the confusion. The copy of the roentgenogram in his article presents large irregular masses in both lower lung fields, which the author states are "lentil-sized foci of calcific density," although lentils are supposed to be smaller than peas and should average 5 mm. in diameter. The history, physical examination and the reproduction of the roentgenogram are at variance with all of the classic cases noted above and we would exclude Klemm's case from our approved list. For details see Case 22, in section of *Summary of Previously Reported Cases.*

It has long been a histopathologic truism that similar or even identical histologic pictures can sometimes be produced by a variety of causes or through diverse processes. Other conditions than true pulmonary microlithiasis can no doubt produce some laminated deposits in the lungs or even in the alveoli, but this does not mean that the condition is pulmonary microlithiasis. A similar situation occurs more frequently when the characteristic histo-

logic lesion of sarcoid is found in the abdomen or in a lymph node. This does not necessarily mean that the patient has the disease sarcoidosis, as other tissue insults can produce the same local histologic reaction (Wolbach, personal communication). For these reasons we feel that the above cases should be excluded from the list of verified pulmonary microlithiasis, and we feel that the classic roentgenographic appearance should be considered essential in the diagnosis.

The situation is much worse, of course, in regard to the accuracy of diagnosis by roentgen examination. There are several widely different agents and conditions which may produce the same roentgen appearance in the lungs. Diffuse miliary lesions indistinguishable from each other, in many cases by roentgen examination alone, may be produced by several different infectious agents, by inhalation of irritant or toxic materials, by metastatic tumors or by other less common causes. Even with all the help possible from the history, the complete examination and the laboratory tests, it may still be impossible to arrive at an accurate decision as to the etiology of a given pulmonary condition. Even biopsy and histologic study fails at times. But, on the other hand, there are situations where the roentgen appearance is highly suggestive, if not characteristic, of a single etiologic factor or condition. In Sharp and Danino's[18] patient, where the needle biopsy was first reported as "haemosiderosis," either the biopsy was inadequate or the pathologist was in error. Before a rare condition can be recognized, there must be previous knowledge that such a condition exists. We can only speculate, therefore, as to how many patients with pulmonary microlithiasis have been seen but not recognized. About half of the cases already reported have been considered to be pulmonary tuberculosis of the miliary type, and some of them were actually admitted to sanatoria and treated for tuberculosis. The important points in differential diagnosis by the roentgen examination have already been elucidated. Before considering the histopathologic details and theories as to etiology, we should summarize the information already available in the medical literature concerning this unusual condition.

SUMMARY OF PREVIOUSLY REPORTED CASES, IN CHRONOLOGIC ORDER, BY DATE OF PUBLICATION

Case 1. (F. Harbitz,[4] Norway, 1918.) A married woman, aged forty-one, who had acute rheumatism as a child and again three years prior to admission; also episodes of pain in abdomen and bleeding from the gastrointestinal tract.

Past History: Shortness of breath, ten years; recent dyspnea and cyanosis; edema of legs, ascites, oliguria and orthopnea, two years. Present Findings: Clubbed fingers, cyanosis, anasarca.

Laboratory Data: Urine showed albumin; blood showed polycythemia, red blood cell count was 8,448,000.

Roentgen Examination: No plate or film of the chest before death. Roentgenogram of slice of lung postmortem showed diffuse calcium deposits.

Autopsy: Heart 400 gm., right ventricle ++, valves normal. Lungs heavy, sank in water. Cut surface felt like sandpaper. Small calcareous granules fell out of dried sections. No calcium deposits elsewhere. Thyroid, parathyroids, spleen, liver, kidneys, stomach, hypophysis and bones all normal. Fallopian tubes tuberculous. Histologic Examination: Typical calcified laminated concretions in lungs only. No evidence of infection. Analysis of ash of lung (78 per cent of weight) showed calcium phosphate 80 per cent, calcium carbonate 18 per cent. Small quantities of iron and magnesium.

Case 2. (Otto Schildknecht,[17] Germany, 1932.) Female, aged forty-five, admitted for psychosis, diagnosed as bulbar paralysis. Died. Wassermann positive. Roentgenograms of the chest revealed numerous miliary shadows generalized but more in lower lobes which were as dense as marble. First thought to be miliary tuberculosis.

Autopsy: Brain atrophy, bulbar paralysis. Lungs were solid, with fine granules in cut surfaces like sand. Histologic Examination: Calcified bodies in alveoli, with onion-like laminations, some with a central nucleus.

Elastic fibers in periphery. Tests for amyloid negative, for calcium positive. Photomicrographs of lungs are typical.

The roentgenogram of this patient's chest is said to be reproduced in the textbook of Schinz, *et al.* (Third Edition, Leipzig, 1932, vol. II, p. 798) as amyloidosis of the lung. Schildknecht reports the case as one of calcified corpora amylacea, but emphasizes the unusual features and expresses a doubt that the lesions are really amyloid in origin.

Case 3. (Ludwig Puhr,[15] Budapest, 1933.) This author described his patient as one having lesions similar to Virchow's "calcium metastases," but different in details, therefore a new and previously unknown condition. He coined the name "mikrolithiasis alveolaris pulmonum" for the disease.

The patient was a female, aged forty-nine, who had pneumonia 7 times, cyanosis on exercise and clubbing of digits. She was re-admitted a year later with cough, dyspnea, cardiomegaly and edema. Sudden exitus.

Roentgen Examination: Fine calcium-containing granules in both upper lobes, with homogeneously dense shadows in the lower three-fourths of each lung.

Autopsy: Lungs heavy, did not collapse, calcium plaques in pleura, cut surfaces like sandpaper. Histologic Examination: Concrements in the alveoli, not in the alveolar walls or arteries.

Puhr concluded that he had found a new disease, one of diffuse multiple tiny stones in the lungs. Chemical analysis revealed the stones to be mostly calcium phosphate.

There were no abnormal calcifications outside the lungs and no increased bone resorption.

Case 4. (B. Mariani, *et al.*,[11] Rome, 1949.) These authors reported the case of a farmer of twenty-eight who was hospitalized at the age of nineteen for severe hemoptysis, diffuse chest pain and fever. He recovered and returned to a normal life. He was admitted to the Institute Forlanini in 1940.

Laboratory Data: Vital capacity was 1,800 cc., Wassermann and Koch tests were negative, tests for fungus were negative, but the Takata-Ara test was strongly positive. Serum calcium was 10.2 mg. per cent.

Roentgen Examination: Numerous fine nodules throughout both lungs apparently with homogeneous opacity in the lower lung fields. Grid films demonstrated micronodular elements about 1 mm. in diameter, making up the basal density. The sputum was tested unsuccessfully for calcium and a pulmonary biopsy was attempted but was insufficient in amount.

Autopsy: The lungs were full of calcareous, onion-like lamellary formations in the alveoli, some of them with central nuclei suggesting cellular elements. There were also areas of ossification in the lungs, some calcification in the alveolar walls and bilateral apical pneumothoraces. There was chronic hepatopathy with fatty degeneration of the liver. Chemical analysis revealed the deposits to be mostly calcium phosphate, but some calcium carbonate was also present.

Case 5. (Friedrich Leicher,[8] Germany, 1949.) This patient, a forty-four year old farmer, had hemoptysis in 1919, shortness of breath in 1937, angina in 1938 and cough with yellowish sputum when admitted in 1943.

Roentgen Examination: Bilateral homogeneous density in the lungs, with numerous fine particles in the upper lung fields.

Autopsy: Numerous laminated bodies in the alveoli, sometimes several in one alveolus, with foreign body giant cells around some of them and islands of bone formation in interstitial tissue. Chemical analysis revealed mostly calcium phosphate and calcium carbonate.

Case 6. The first case in the radiologic literature was reported by W. Lindig[9] from Germany in 1951. This was the case of a forty-year old gardener with classic roentgenograms, and Lindig emphasized the striking discrepancy between the roentgen findings and the lack of pulmonary symptoms. The patient's vital capacity was 2,900 cc., his serum calcium 8.8 mg. per cent and the Wassermann and Koch tests were negative. He had worked for one year with a compressed air hammer in basalt stone work, which was thought to be of possible etiologic significance.

The roentgenograms were regarded by Lindig to be characteristic of the condition and he predicted that the chest films could be considered sufficient for accurate diagnosis. His films revealed diffuse densities throughout both lungs, appearing homogeneous below the third interspaces, but clearly showing small numerous sand-like particles of equal size and configuration in the upper lung fields.

Bilateral pulmonary biopsies were done, revealing tiny laminated calcium deposits in many of the alveoli. Lindig believed that in the future the diagnosis might be made by finding the microliths in the patient's sputum, and that the diagnosis could equally well be made by roentgen examination alone. This patient was still living and asymptomatic at the time of the report.

Case 7. (Benard, *et al.*,[2] France, 1950.) This case of a seventy-two year old male has already been mentioned as being somewhat doubtful, roentgen examination being reportedly negative, both by fluoroscopy during life and also by roentgenography of the lung at autopsy. Otherwise, the description of the autopsy and of the histologic findings could fit the disease.

The patient was essentially symptom free before his final illness, which was a ten day fever with slight dyspnea. Four days after his temperature returned to normal he died suddenly in a crisis suggesting pulmonary edema.

Autopsy: Numerous oval or circular particles in the alveoli. Their centers were acellular and there were concentric layers like those of an onion. They presented a dark cross by polarized light, and they stained red with alezorine. There was no reaction in the alveolar walls. Blood vessels and connective tissue appeared normal.

Benard and his co-workers compared and contrasted this case with those of Mariani, *et al.* (Case 4 above) and Puhr (Case 3), then decided that it was different symptomatically and roentgenographically. If this is a true case of microlithiasis, this is the oldest patient in the series.

Case 8. (Sharp and Danino,[18] Swansea, Great Britain, 1953.) This is the first case reported in the English literature, one already referred to as having been misdiagnosed "haemosiderosis" on needle biopsy. Sharp and Danino give an excellent description of the pathologic and histologic findings, using excellent illustrations.

The case is that of a fifty year old housewife, married but childless, who was followed from 1945 to 1949 when she died and was autopsied. Her symptoms were those of gradually increasing shortness of breath, cough, pleurisy and pneumonia. Her laboratory tests were all essentially normal except for slight polycythemia.

Roentgen Examination: The findings were most unusual. The lung fields were almost completely opaque, with fine discrete miliary densities visible individually only at the periphery. There was no demonstrable change in the roentgen appearance from 1945 to 1949.

Autopsy: This revealed the typical alveolar microlithiasis, described as "calcospherites." There were nodules of bone in portions of the lungs and in the pleura. No hemosiderin could be demonstrated. The kidneys, thyroid, adrenals, ovaries, lymph nodes and hair were all normal. No tuberculosis or fungus infection could be found. Also discovered at autopsy was an old rheumatic disease of the mitral valve with "moderate" stenosis. This led the authors to speculate on the relationship between the two diseases, and probably led them to include the cases of Jona[43] and Munk[48] which we believe are not true alveolar microlithiasis.

Chemical analysis of portions of the lungs revealed excessive calcium and phosphorus, mostly as calcium phosphates. The iron content was only 0.037 per cent of the dry weight compared to Munk's case with 4 per cent of iron in the dried lung.

The same patient was later (1955) reported by J. Gough[3] from a different viewpoint, by aiming to correlate the roentgenologic and pathologic changes in some diseases of the lungs. In his paper, Gough compared and contrasted the changes seen in mitral disease with hemosiderosis and those seen in alveolar microlithiasis, as well as other conditions.

Four articles on microlithiasis appeared in 1954, reporting 7 cases, among them the first recorded instance of multiple cases in one family.

Cases 9, 10, 11 and 12. These were reported by Mikhailov[13] from Bulgaria. His patients were a fifteen year old girl whose roentgenograms were considered to be typical of microlithiasis and 3 members of a family all with similar roentgenograms; a thirty-two year old woman, proved by pulmonary biopsy, her forty year old brother, and his seventeen year old son. Neither of the latter 2 was proved by biopsy but had identical roentgenographic changes.

Case 9. This girl, aged fifteen, suffered from cough, fatigue, weakness and clubbed fingers.

Laboratory Data: Hypercalcemia (17.7 mg. per cent); vital capacity 500 cc.; and Takata-Ara test positive. Crystals of calcium oxalate were found in the urine. A liver biopsy was done and a chronic nodular inflammatory process was found, with fatty degeneration.

Roentgen Examination: Very dense lungs, apparently homogeneous in the bases, but with multiple separate calcific densities in the upper lung fields. The heart borders were obscured. The skeleton appeared normal. There was no change over a two year period.

Case 10. This was a thirty-two year old woman who complained of weakness and a slightly productive cough.

Laboratory Data: Vital capacity was 1,200 cc.; blood calcium varied from 11.4 to 14.6 mg. per cent and the Takata-Ara test was positive. Crystals of calcium oxalate were identified in urine sediment.

Roentgen Examination: Micronodular calcifications in the upper lungs, increasing in density toward the bases. A skeletal survey was negative.

Histologic Examination: Both liver and lung biopsies were obtained. The liver specimen revealed a chronic nodular inflammatory process, while the lung tissue showed the typical laminated calcified deposits in many alveoli. In places, the alveolar epithelium was atrophic or degenerated, and in other areas bone formation was found. Chemical tests indicated calcium phosphate and carbonate, but no iron.

Case 11. This forty year old brother of Case 10 had been rejected for military service for alleged miliary tuberculosis, presumably on the basis of roentgen examination. He gave a history of four previous attacks of pneumonia. He complained of weakness and also clubbing of fingers and toes. There was a questionable history of malaria and of hematemesis.

Laboratory Data: Vital capacity 2,300 cc.; blood calcium 10 mg. per cent; Takata-Ara test positive and again crystals of calcium oxalate in the urinary sediment.

Roentgen Examination: The findings appeared identical with those of his sister, with micronodular shadows seen best at the periphery and confluent densities at the bases of the lungs. A skeletal survey was negative. No biopsy was performed.

Case 12. This seventeen year old boy, the son of Case 11, presumably asymptomatic, was found by survey films of his chest to have the same micronodular densities in his lungs, with some larger nodules in the right apex and left infraclavicular region.

In all 4 patients the Wassermann and Koch tests were negative, and bacterial studies of sputum were also negative. All patients lived together on a farm, and Mikhailov speculated on exogenous agents and endogenous factors as possible etiologic causes and felt that the liver involvement was part of the picture. He postulated an infection taken in through the mouth to the intestinal tract to the liver and then the lungs as the most probable cause.

Case 13. This case was reported by A. Manz[10] from Hamburg, Germany. It was that of a thirty-seven year old woman who was first seen as a child of twelve with cough, clubbed fingers and unusual roentgen findings of fine diffuse granulated shadows through both lungs fields, more intense at the bases. The case was discussed with a diagnosis of "bronchitis obliterans with diffuse bronchiolectasis" in the book "Kindertuberkulose" by Simon and Redecker at that time (1927).

The patient married at the age of twenty-two, had two children, and led an uneventful life until her final admission in 1952 with cardiac decompensation. She died three days after admission.

Roentgen Examination: A chest film in 1941 revealed no definite change in the pulmonary condition compared with the films in 1927. Roentgenograms of the patient's mother and one brother were negative, one other brother refused examination.

Autopsy: Right heart failure, ascites, clubbing of the digits, and solid dense lungs which felt like sandbags. Histologic examination: This revealed onion-like concrements diffusely distributed in the alveoli, with fibrosis of the interstitial tissues and cellular infiltration. A dark spot of unknown nature was present in the center of most of the concrements. Amyloid tests were negative. Tiny rods were also seen, thought to be calcified fungi. Chemical analysis of lung tissue revealed a marked increase in ash, high percentage of calcium, also 7 per cent aluminum and 4.4 per cent magnesium.

Manz interpreted the case as one of chronic fungus infection ending in pulmonary microlithiasis. This is the longest known duration of the condition—25 years.

Case 14. This case was reported from Budapest by Petrányi and Zsebök.[14] It was that of

an eight year old boy who was hospitalized in 1947 for chronic miliary tuberculosis, but because of the discrepancy between the roentgenograms and a state of good health a biopsy was decided upon. The histologic findings were considered to be unusual, possibly representing amyloidosis or atypical miliary tuberculosis. The diagnosis of alveolar microlithiasis was not made until 1952.

The patient had pertussis at 6 months, then chronic bronchitis, next, pneumonia at 18 months and again at 3 years, with a continued chronic cough.

Roentgen Examination: The findings in 1952, 5 years after discovery of his pulmonary condition were essentially the same as in 1947, revealing symmetrically distributed kernels of sand, most marked in the bases of the lungs. A skeletal survey was negative.

Laboratory Data: Vital capacity 2,390 cc. (calculated 3,550); CO_2 consumption from air 206 cc. per minute (normal); Takata-Ara test slightly positive; alkaline phosphatase 6.13 Bodansky units; serum cholesterol 152 mg. per cent.

Tests for amyloid were negative. The histologic appearance was typical, showing onion-like structures filling the alveoli, with only moderate interstitial fibrosis, and in some areas true bone formation including haversian canals.

The authors state that the case was roentgenologically recognized and histologically proved, and suggest that biopsy may not be necessary if the roentgenograms are typical.

Case 15. This case was the first to be reported from Japan, by Takahashi[19] and, like Case 14, was that of a boy of eight when first seen. His condition was discovered by a chest survey film in 1951 and was called miliary tuberculosis. His tuberculin test was negative in 1951 but became positive in 1952 although he had no symptoms except cough on exercise. Roentgen examination of the chest was repeated in 1953 with essentially the same findings, bilateral diffuse miliary densities. His liver was palpable but liver function tests were normal. His condition was identified after biopsy of the right apex in 1953. The histologic picture was that of numerous tiny granules with lamellary structure in the alveoli. They gave a positive reaction to stains for calcium and chemical analysis showed mostly phosphates, some carbonates. The serum calcium was 10 mg. per cent. The basal metabolic rate was first plus 31, later plus 26.5.

Six new cases were reported in 1955 in four separate articles, one of them being a report of 3 cases in one family, the second instance of familial occurrence of this disease. All reports appeared almost simultaneously so that it is difficult to be sure of the exact chronologic order, but that is of no real importance.

Case 16. This case was reported by Badger, *et al.*[1] and is the same Scotsman we are reporting as Case 1 in our series. The details have already been given above.

Cases 17, 18, and 19. (Reported by Kei Sato[16] from Tohoko University, Sendai, Japan.) These were three sisters aged nineteen, ten and six. The latter is the youngest one reported so far. The father of these girls had died several years previously of pulmonary tuberculosis, but his clinical record and roentgenograms (if any) were not available. The parents of these three girls were germane cousins. The mother's chest was normal and the remaining sister had not yet been examined at the time of the report. The father was one of six brothers, one of whom had tuberculosis. The mother had four sisters (one died of cancer) and one brother.

Case 17. This was the oldest sister (nineteen years of age) who was found to have a negative skin tuberculin test in a survey in 1946, was inoculated with BCG, and converted to positive in 1947, remaining so until 1951. At a mass chest survey in 1952, she was diagnosed as having miliary tuberculosis and immediately hospitalized for four months' therapy with streptomycin, PAS and INAH in combination. She was discharged to her home, but there was no change in the disseminated pulmonary lesions so that she was re-admitted in 1954, microlithiasis now being suspected.

She was well-nourished, had no symptoms, and extensive clinical and laboratory examinations were within normal limits. These included blood chemistry, electrocardiography, pulmonary function tests, cardiac catheterization and spinal fluid study in addition to the usual blood and urine tests and sputum examination. Biopsy was performed and it was found that the pleura was adherent and the surface of the lung was rough and granular. Extensive cultures for bacteria and fungi were made from ground-up lung tissue, but all were negative, as was a guinea pig inoculation with some of the suspension.

The histologic appearance was typical—that of translucent minute laminated balls in the alveoli. Test for iron was negative, chemical analysis showed calcium phosphate and oxide predominant, with 2.8 per cent MgO and 0.93 per cent SiO_2 in the ash.

Her roentgenograms revealed minute miliary lesions in both lungs, more dense around the hila and in the bases, with individual lesions more clearly seen superiorly and peripherally.

Case 18. This was the ten year old sister of Case 17, said to have had pneumonia in infancy and to be subject to colds. Her tuberculin reaction turned positive at the age of five without inoculation. Her physical examination and laboratory tests were all close to normal. Vital capacity was 1,650 cc., 15 per cent below her calculated normal. Gastric washings were negative for tubercle bacilli on culture.

Her roentgenograms were strikingly similar to those of her sister, but less dense at the bases and the individual shadows appeared more minute. Thickened interlobar fissures were quite definite.

No biopsy was obtained and no therapy instituted.

Case 19. This was the youngest sister of Cases 17 and 18, aged six. Her past history was unimportant. Her clinical examination was negative. The tuberculin skin test was positive. Cultures of her sputum were negative for tubercle bacilli.

Her roentgenograms revealed the same disseminated miliary lesions, similar in amount and degree to those of her sisters. No biopsy was taken and no therapy given.

Case 20. This case was also reported from Japan by Hirota and seven colleagues.[5] It concerned a seventeen year old male who had no symptoms except chest pain. A chest roentgenogram in 1953 was interpreted as miliary tuberculosis, and he was admitted and treated with streptomycin and PAS. A repeat roentgenogram in 1955 showed no change and a lung biopsy was performed revealing microlithiasis.

His vital capacity was 1,640 cc., considerably reduced below his calculated normal. Maximal breathing capacity was 51 liters/min. The basal metabolic rate was plus 2. Bronchial washings were negative for acid fast bacteria. Albumin-globulin ratio was 1:1, with lowered albumin. Serum calcium was 12 mg. per cent.

The roentgenograms showed a diffuse dense miliary process, apparently typical of microlithiasis.

The biopsy demonstrated laminated stones in the alveoli, measuring 170 to 440 micra in diameter. There were some round cell infiltration in the interstitial tissue and thickening of the pleura. No tuberculous lesions or fungi could be demonstrated.

Chemical analysis of portions of the lung showed no silica, but increased calcium, phosphorus, sodium and magnesium. The calculi were mostly calcium phosphate with some calcium carbonate.

Case 21. This case was reported in Nov., 1955, by Kent, Gilbert and Meyer.[6] It concerned a Mexican laborer "born in Dallas, who otherwise was perfectly well" (*sic*), aged thirty-five, with a history of repeated hospitalizations for alcoholism. During one of these bouts, in the spring of 1954, a routine chest roentgenogram was made and interpreted as "miliary tuberculosis." He was transferred to a sanatorium and received chemotherapy for four months, when he left the hospital. He was later admitted to another sanatorium in February, 1955.

The patient gave a history of measles as a child and a chancre in 1935 with inadequate treatment. He had worked as a cotton picker from 1931 to 1937 and in a fertilizer factory from 1937 to 1942 where he handled sulfur rocks which were later ground up and mixed with earthy material. In this work he had to wear a mask because of the high concentration of dust. He later worked in a rug factory, exposed to cotton and wool dust, then from 1946 on in restaurants.

His physical findings were negative. Tuberculin and histoplasmin tests were both positive. Serum calcium and phosphorus were normal. The Wassermann test was doubtful. Spinal fluid protein was 84 mg. per 100 cc. All bacteriologic studies, and biopsies of the liver, scalene node and bone marrow yielded negative results. Roentgen survey of the skeleton was negative. Roentgenograms of the chest presented a striking appearance of numerous fine diffuse granular nodulations pervading both lung fields. The greatest density was toward the lung bases, where the cardiac and diaphragmatic outlines were obscured. Bucky roentgenograms brought out better detail, revealing

a heart of normal size, and individual lesions strongly resembling particles of sand. Pleural thickening was evident in both bases. No cavities could be seen.

Biopsy of the lung was performed through the right fourth anterior interspace, where the lung was found to be free except for a few scattered adhesions. The lung surface felt granular and gritty. Histologically about one-third of the alveoli contained concretions morphologically similar to corpora amylacea, ranging in size from 0.02 to 0.3 mm. in diameter. They were laminated and some areas contained bony lamella. Many alveoli containing the calculi had normal walls, but more often the walls were thickened. Special stains proved that the bodies were calcified. They contained doubly refractile lipids, and a positive colloidal iron stain suggested the presence of acid mucopolysaccharides. The concretions did not contain amyloid material or iron. Some calculi appeared younger and smaller than others and not yet calcified.

The patient remained asymptomatic and in excellent physical condition and was discharged. Since then he has been working full-time.

The emphasis in this first paper is on the pathologic and histologic aspects of this case. Just recently (July, 1956) a second report of the same case appeared[12] giving more detailed studies from the clinical laboratory and placing more emphasis on the clinical aspects of the disease. The authors justly conclude that the roentgen appearance is so characteristic that the condition should be recognized on sight.

Case 22. The case recently reported by Klemm[7] from Rostock in East Germany, concerns a fifty-nine year old farmer who was first seen in 1927 because of a goiter. Chest roentgenograms at that time revealed generalized pulmonary lesions and re-examination in 1938 yielded a report of "miliary pulmonary lesions unchanged since 1927." In 1940 his goiter was partially removed, and in 1954 he was admitted to the Rostock Hospital for biopsy of the remaining goiter, tumor being suspected.

Physical examination revealed cyanosis of the face and upper extremities, a vital capacity (sitting) of 2,700 cc., serum calcium of 14.5 mg., but all other tests were negative. Chest roentgenograms were described as showing miliary lesions, confluent in the lower lobes, less toward the apices, with "lentil-sized foci of calcific density" visible on high voltage films.

At one time he had been in a sanatorium with presumed pulmonary tuberculosis, apparently not confirmed. There had been four biopsies of his colloid goiter, with suggestion of early malignant change. Lung biopsy was not performed "as it symptomatically was not indicated."

Our opinion after reading the original article and studying the reproductions of the roentgenograms is that this is *not* a case of the classical pulmonary alveolar microlithiasis on the evidence as presented and should not be included unless it is subsequently proved by biopsy or autopsy.

SYMPTOMATOLOGY

Most diseases, particularly the pulmonary ones, produce symptoms at the onset or early in their course. The majority of all patients come to their physicians because of symptoms, either local or general. In this disease the striking thing from the clinical aspects is the fact that most of the 45 patients (Case 16 of the published series is the same as Case 1 in our series) have been picked up more or less by accident, and only a minority (17) had symptoms when first seen by a physician (1 was found at autopsy). The larger number (28) was found by "routine" roentgen study, either for admission to the Armed Forces, a pre-employment examination, a chest survey program, or routine survey of families for similar pulmonary shadows. In the 21 published cases (Case 16 is omitted since it is Case 1 in our series) 9 had symptoms when first seen by a physician, 11 were found by "routine" roentgenograms and 1 patient had no roentgen examination before autopsy (Harbitz,[4] 1918). By contrast, only 7 of our 24 unpublished cases had symptoms when first seen, 4 were discovered by routine roentgenograms in the Armed Forces, 1 by pre-employment roentgen examination, 6 by "survey" films and 6 by examining the families of known cases.

Symptoms in this disease seem to be latent for an indefinite length of time, "indefinite" because the date of onset of the

condition is unknown. They are more common in the older patients, more often absent in the younger ones. The most frequent symptoms are those of pulmonary insufficiency, shortness of breath on exertion usually being the first to appear, then increasing dyspnea, cyanosis, cough, increased sputum, occasionally clubbing of the digits and finally heart failure due to cor pulmonale. It is not known how long it takes to progress through these stages but it seems to be a variable length of time depending upon unknown factors. The evidence suggests that the process is a continuing one, *i.e.*, that the microliths continue to form and perhaps also increase in size as the disease progresses rather than appear as a single massive deposit at one time. Kent, *et al.*[6] report microliths varying both in size and age, some of them still uncalcified.

Twenty-eight of the 45 patients (17 out of our 24 cases) had no real symptoms when first seen. "Cough" is a nonspecific and very common complaint, common to everyone at some time or other in his life. There was nothing unusual about the cough in the early stages of this disease, and only the usual productive cough without raising blood or pus was noted in the later stages when heart failure and pulmonary congestion were superimposed on the pulmonary deficiency. There was no history of raising excessive mucus as may occur with pulmonary adenomatosis and only 3 cases had hemoptyis. An opportunity to make the diagnosis without biopsy occurs occasionally when the patient raises some of the microliths in his sputum. It would be possible to identify them under the microscope. As so often happens in medical practice this bit of information is usually not volunteered by the patient but is obtained only by direct or leading questions.

Physical examination has been most disappointing in these patients, the findings being uniformly within normal ranges in the earlier stages, and nonspecific in the advanced cases, even after viewing the amazing roentgenograms. However, the established facts of negative physical examinations and paucity of symptoms are of value, as they form a constant and important part of the total picture of this rare disease. Almost any other disease or condition resulting in such massive involvement of pulmonary tissue would give striking symptoms and signs of its presence. The one common exception is, as mentioned above, pulmonary sarcoidosis.

The laboratory findings have also been remarkably unproductive, most of the routine ones being entirely within the normal ranges (with a few exceptions which could possibly be the result of imperfect techniques). In the later or advanced stages of the disease there may be a compensatory or secondary polycythemia, due to loss of pulmonary function. The electrocardiographic findings were normal in practically all of the patients except again those in the symptomatic stage who might have the evidence of right ventricular hypertrophy (cor pulmonale) in their tracings.

Nothing constant or of any apparent import was found in the blood cell counts, the blood proteins, the calcium, phosphorus or phosphatase contents of the blood or in the many other types of chemical analyses which were performed. The urine, sputum, gastric washings, bronchoscopic aspirations, and even the results of venous catheterization of the heart in two cases, were likewise non-contributory. Extensive and elaborate tests of pulmonary ventilation and physiology measured the damage done to the alveolar bed, but in others, perhaps earlier cases, were remarkably close to normal in spite of obvious extensive pulmonary involvement. No clues were obtained from any of the examinations or tests as to the cause or mechanism of production of the condition nor as to its etiologic factors, if any.

There was no significant difference in sex incidence, 21 males and 24 females being involved. Racial factors or predominance were not evident, the disease being reported in one or more of the following: Norwegian, English, Scots, Irish, French,

Italian, German, Bulgarian, Hungarian, Spanish, Negro, Japanese, Armenian and Mexican.

The age distribution at the discovery of the disease was fairly wide but all patients except 3 have been under fifty-three years of age with the majority (21) between thirty-one and fifty years. The oldest patient, aged seventy-two, is the doubtful case of Benard, *et al.*[2] In the past two years (1954–1955) the average age level has been lowered considerably by the finding of several asymptomatic cases in children. The youngest was the girl of six, reported by Sato[16] but there have also been reports of 3 patients, one 8 years of age[14,19] (Case 23) and one each of 10 and 12.[10,19] Nine patients under twenty have been reported including those noted above.

The longest known duration of the disease in any one individual is the case reported by Manz[10] where the pulmonary abnormality was first discovered at the age of twelve with death occurring 25 years later at the age of thirty-seven. A note is made that there was no definite change in the pulmonary condition by roentgenograms between 1927 and 1941. There are several other patients who have been followed 10 to 15 years, some of them until exitus, but also several of equal duration who were still alive and symptom-free at the time of this report.

There has been no constant or consistent occupational exposure in this group, and the discovery of several cases in young children makes it highly improbable that anything in the ordinarily accepted group of industrial diseases is concerned. On the other hand, some of the patients have been farmers and others have lived on farms which raises the possibility of fungi or yeasts as possible etiologic agents. Against this is the fact that identical lesions have appeared in patients who have lived all their lives in cities, and, more important, the inability of anyone to demonstrate pathogenic fungi or yeasts in any of the autopsy or biopsy specimens, although many such attempts have been made. The sole exception is the case reported by Manz[10] who interpreted some small rounded chain-like rods in the lungs as calcified fungi.

Antecedent disease was consistently absent both by history and by autopsy studies. Several of the patients gave stories of repeated attacks of pneumonia or pleural pain but the disease was probably already present and well advanced when these occurred. Almost invariably the symptoms of pulmonary difficulties *followed* the onset of the condition rather than preceded it. There has been no convincing evidence by autopsy in 11 cases and by history and various tests in the other cases of any antecedent or even co-existent disease. The one exception is the finding of healed rheumatic heart disease with mitral stenosis in Sharp and Danino's patient.[18] Even in this case the mitral stenosis was of only mild degree and in all probability had nothing to do with the pulmonary microliths. (Chemical analysis revealed only a trace of iron in the lungs, instead of the 4 per cent or more commonly found in pulmonary hemosiderosis due to mitral stenosis.) The mitral valve in their case "readily admitted the tip of the index finger," which would correspond to a valve orifice of 3 sq. cm. and not the "tight" valve (1.0 sq. cm. or less) usually found with diffuse pulmonary changes. Badger, *et al.*[1] repeated the mistake by Sharp and Danino of including the cases of Jona and Munk (*vide supra*) and even compounded it by listing them in their Table 11 as "Healed Right-Sided Heart Disease" (sic).

Other associated or concurrent diseases were conspicuously absent except in two of Mikhailov's patients who had granulomatous lesions of unknown etiology in the livers found by biopsy, quite different histologically from the pulmonary lesions. Two other patients had positive Takata-Ara tests, suggesting something wrong with the liver but not too reliable or dependable for decisive conclusions.

Renal calculi were found in our Case 1, both during life and at autopsy, naturally

suggesting the possibility of parathyroid dysfunction, but this was not confirmed by exhaustive tests nor by autopsy. So far no other patients have been found to have renal calculi and only one (our Case 3) had a suggestive history.

Environment has apparently not been important except for the suggestion that farming or rural life might be a contributing factor. Some of the patients lived in hilly or mountainous areas, others at medium altitude, and some at sea level. Some were in tropical areas, others in temperate zones and 3 in Canada. No cases have been reported from South America, Africa or Sweden as yet. A cursory survey of the geologic formations and the chemical constituents of the dominant rocks in the areas where the cases arose gave us no leads.

PATHOLOGY AND HISTOLOGY

Of the cases reported so far (21) including the ones in this report (23 new cases), 11 have been proved by autopsy, 11 by pulmonary biopsy, leaving 22 proved only by the characteristic roentgenograms plus the supporting facts in the history. Particularly important in these cases are the familial occurrence, the absence of previous pulmonary disease and the absence or relative lack of symptoms until the terminal stage is reached.

The classic histologic picture is naturally the most reliable factor in the diagnosis but it may be unrecognized or even misinterpreted. Similar but not identical histologic appearances may erroneously be interpreted as being due to this condition.[17] In all cases correlation of pathologic and roentgenologic findings is essential as advocated by Gough.[3] The gross distribution and anatomic arrangement of many pulmonary lesions can best be studied by good roentgenograms, while the histologic detail can be elucidated by biopsy, differential stains and special techniques.

According to the autopsy reports so far available, the gross pathology in this particular condition is apparently limited to the lungs. No constant or consistent involvement of other organs has been found. In one case[17] a healed rheumatic mitral disease was noted and in another case renal disease with numerous small calculi was confirmed at autopsy. In two patients[13] liver biopsies revealed evidence of a "chronic nodular inflammatory process with dystrophic changes and fatty infiltration." In two others the liver at autopsy showed fatty degeneration, but in the remaining it showed only chronic passive congestion or it was normal.

The heart as previously suggested, with one exception, either exhibited dilatation and hypertrophy of the right ventricle in those patients who passed through the stages of right heart failure, or was considered to be normal.

In all cases, as far as we can discern, studies of the kidneys were non-significant except for the calculi in the case of Badger *et al.*[1] Urinary calculi are not mentioned in any of the other autopsies. The gastrointestinal tracts have not been abnormal and special mention was made in several cases that no calcium deposits were found in the kidneys or stomachs of those coming to autopsy.

Of particular interest, because of the repeated suggestions that the disease is due to some abnormal calcium metabolism, were the uniformly negative findings at autopsy in the endocrine glands, the parathyroids, thyroids, pituitary glands, adrenals, ovaries and pancreas.

The osseous skeleton was examined several times at autopsy and was considered to be normal as it has consistently been by roentgen surveys. The spleen and lymph nodes have not been enlarged or abnormal in detail and have not been found to contain calculi or abnormal calcification except as noted in our Case 21.

The Lungs. The major and probably the only primary involvement in this disease was found in the lungs in all cases. In most of them either at autopsy or biopsy, the pleural surfaces were free, but the sand-like particles could be seen and felt immediately

beneath the pleura. In others, only a few adhesions were present, with nothing to suggest an inflammatory reaction. The patient of Badger, *et al.*[1], however, had dense fibrous adhesions obliterating the pleural cavities. The lungs were hard, gritty, solid, did not collapse on removal from the body and were much heavier than normal. In some cases the note was made that the lungs sank in water. The lungs were "still, white, hard and incompressible. They felt like stone. They were astonishingly heavy, weighing together 4.020 gm."[17] In most cases there was a distinct differences between the apical and basal portions. The former were softer, semi-compressible and sometimes emphysematous, while the bases were stony hard and only the extreme margins were compressible. The softer portions could be cut with a knife although with some difficulty and with a marked gritty feeling. The lower harder portions had to be cut with a saw. All reports stress the fact that "the cut surfaces felt like sandpaper" and many reports mention that they were relatively bloodless. Purulent exudates, infarctions, consolidations, cavitations and hemorrhages have been conspicuous by their absence. Emphysematous blebs, however, have been common in the apical portions and along the anterior margins, and have been mistaken for cavities or pneumothoraces on roentgenograms. The cut surfaces did not give positive Prussian blue reactions. Decalcification was difficult, slow and prolonged with acids, requiring either 20 per cent nitric acid or the electric method.

All of the cases with exception of the one of Benard, *et al.*[2] have shown extensive, unusual and consistently similar calcium deposits in the alveoli. There have been numerous reports of metaplastic new bone formation in the lungs sometimes closely associated with, but at other times separate from, the "calcospherites." The interstitial tissues of the lungs were apparently normal in some individual sections, but in others showed either fibrosis or cellular infiltration or both. The alveoli themselves have been normal in many cases although containing laminated concretions. In some cases it was estimated that one-third or one-fourth of the alveoli contained stones, while in others it seemed that 75 per cent to 80 per cent of the alveoli contained calculi. In general, on reviewing all of the records, it seems quite probable that both the numbers of calculi and the amount of tissue reaction increase either with the age of the patient or with the known duration of the disease.

Excellent descriptions in English of the histologic details in the lungs accompanied by good photomicrographs are available in several of the articles written by pathologists, particularly the ones by Sharp and Danino[18] and by Kent, *et al.*[6] Summarizing their opinions and descriptions it seems that the concretions, calculi or calcospherites, whatever they may be called, are quite similar in appearance to the corpora amylacea most commonly found in the prostate gland. They also present some of the same structure or morphology, being made up of irregularly concentric rings or laminations, which take different intensity of stains. They usually vary in size from 0.02 to 0.3 cm., and may have radial lines suggesting cracks crossing the circular or oval rings. Some of them have a central nidus which is not yet identified but could be tissue debris. The corpora produce a Maltese cross pattern when viewed by crossed Nichols prisms. As previously suggested, the variation in size may correspond to a variation in age, as some of the smaller bodies do not appear to contain calcium.

The descriptive words "in layers like an onion" or simply "onion-skin appearance" are found in nearly all histologic reports and are quite appropriate.

The bodies, according to Kent, *et al.*,[6] "contained doubly refractile lipids, and a positive colloidal iron stain suggested the presence of mucopolysaccharides." They did not contain amyloid material or iron. No cellular remnants could be identified in them. There was no regular arrangement or

pattern to fit an anatomic structure or distribution. Giant cells were common, but seemed to be haphazard in location. No one so far has been able to demonstrate bacteria, fungi or yeasts, except Manz,[10] and in his case they were not confirmed by culture or differential stains.

CHEMICAL AND SPECTROGRAPHIC ANALYSES

Chemical analyses of the lungs have been made on nearly all of the autopsied cases and on some of the biopsy specimens. We have had several of the analyses repeated and, in addition, have had some of the individual microliths analyzed by chemical and physical methods including spectrography.*

All analyses show a marked increase in the total solids and in the ash content of the lungs, the latter 12 times the usual amount in Puhr's case and even higher in others. All analyses agree that the predominant elements are calcium and phosphorus, with smaller amounts of magnesium and aluminum, and traces of silicon and iron. One of our own analyses of the dried microliths taken from Gough's section 21467–49 was as follows:

Element	Percentage Content of Particulate Weight
P	10.0
Ca	6.3
Mg	0.5
Na	0.3
Fe	0.1
Al	0.01
Sr	0.01
K	0.06
Co, Ni, Cr, Pb, Zn and Si—none found.	

Other analyses correspond to this in general with some variation in calcium-phosphorus ratios, but all agreeing in the almost complete absence of silicon and iron. This is particularly important in differentiating this condition chemically from cases of silicosis and hemosiderosis where the content of silica and iron are respectively much higher.

Analyses for chemical structure also agree quite well, revealing that the calculi consist chiefly of calcium phosphate and a smaller amount of calcium carbonate. They seem to be similar to bone and even more closely allied to the majority of urinary calculi. The major constituent of the microliths is apatite, a tricalcium phosphate, in one or more of its many forms, chiefly $Ca_3(PO_4)_2$. Dr. Prien suggested that the microliths were probably a mixture of hydroxyl-apatite and carbonate-apatite. The percentage difference in calcium and phosphorus between the various forms of calcium phosphate, particularly tricalcium phosphate (which rarely occurs in pure form) and apatite is very small indeed, but the way in which the atoms are hooked together is quite different. Dr. Nichols found the CO_2 value to be slightly higher than the usual value for bone, but the calcium and phosphorus were within the ranges usually found in bone.

The analysis of the dried lung in Leicher's case[8] was fairly representative of the group as a whole and gave the following results:

	Per Cent
$Ca_3(PO_4)_2$	66.5
$CaCO_3$	8.6
$MgCO_3$	1.7
H_2O	5.7
Organic material	17.5
Total	100.0

We feel that reports of analyses in this form are only an approximation. The analyses are actually made for the various ions involved and not for the salts themselves. With such data about ions in hand,

* The dry microliths were removed from a Gough section under a dissecting microscope. Tissue was furnished us by Dr. Badger and by Dr. Sato for analysis and sections. The chemical analyses were made by Dr. George Nichols in the Department of Biochemistry at Harvard Medical School and the spectrographic analyses were done in the Biophysics Research Laboratory of the Peter Bent Brigham Hospital by Dr. Bert L. Vallee and associates. Petrographic studies of the microliths were also made by Dr. Edwin L. Prien of Boston.

one then decides which salts are likely to be present, and the ions are divided up in such a way as to make them come out even. To us this approach can be misleading since the salts very probably do not exist as such. Instead, the ions are arranged in a crystal lattice whose physical pattern may be quite constant but whose exact ionic content may vary within large limits depending upon the conditions under which the crystallization was formed. We think it would be better to report the analysis in the form of totals of ions rather than as salts for these reasons.

Hirota, *et al.*[5] report analyses for potassium, sodium and calcium in their case compared with similar analyses of a normal lung, and calcified tissue from a tuberculous lung. Their results are:

Lung Tissue	Percentage by Weight		
	K	Na	Ca
Normal lung	.14	.42	0.24
Tuberculous tissue	.05	.15	2.0–2.5
Lung, their case	.10	.66	8.2
Dry tissue, their case	.10	.76	9.4

Neither the chemical analyses nor the spectrographic studies gave us any clues as to the etiology or mechanism of this disease but they did give rise to interesting speculations.*

DIFFERENTIAL DIAGNOSIS

Many of the important points leading to a correct differential diagnosis have been mentioned above, but they are worth elaborating and emphasizing at this point. In a previous paper,[65] one of us has discussed the great difficulty which faces both radiologist and internist when they find a diffuse or so-called miliary process in the lungs. It is easy to demonstrate the process roentgenographically and to follow its course, but often impossible to suggest an exact diagnosis either morphologically or etiologically. Even with all of the history, physical examinations and laboratory tests, the decision may still be impossible. The number and variety of miliary proceses in the lungs which simulate each other has been estimated as high as 60[32] and as low as 10.[63] The true number of identifiable conditions varies, of course, depending on the excellence and completeness of the roentgen examination, the acumen and the experience of the observer, the thoroughness of the history and the laboratory tests, and the changes which may occur with the passage of time. The most reliable method is pulmonary biopsy, provided the microscopic picture is recognized by a pathologist who knows this disease. In these 44 cases several instances have occurred where the histologic appearance was either unrecognized or misinterpreted. Many more mistakes were made, however, in assaying the roentgenograms. About half of them were called miliary tuberculosis and many other tentative diagnoses were made, varying from lipiodol emboli in the lung, through pneumoconiosis and fungus infections to inhalation of chalk dust by the school teacher (Case 18). One of the best interpretations of the roentgenographic appearance was the one by Dr. George W. Holmes in 1931 (Case 17) who described the condition as "Pulmonary calcinosis." This descriptive cognomen was repeated by Dr. Sidney Morrison in Case 1 in 1942 and is, in fact, still a good synonym for the process. Only in the past few years has the correct diagnosis been made from the roentgenograms, probably first by Mikhailov from Bulgaria in 1954, who was also the first to note familial occurrence.

There are several exceptions to the general rule according to which diffuse miliary processes in the lungs are difficult to separate one from another and to identify by the roentgen examination alone. Pulmonary alveolar microlithiasis is one of them. There are certain characteristics of distribution of the lesions, their individual and total density and their particular anatomic detail and arrangement which

* For normal standards we used the tables published by Shohl.[64]

cannot be duplicated by any other disease as far as known at present. The clue to the correct interpretation is the demonstration and recognition of innumerable tiny granules of calcific density diffusely and uniformly spread throughout both lungs, less pronounced in the upper lung fields and most marked in the bases medially where the sum total of the calcific density usually obscures the borders of the heart and often also the diaphragms. Overexposed or overpenetrated films may be necessary to bring out the calcific density. In only one of our 24 cases was there any doubt about the correct diagnosis on the original film, and that was in Case 12, in which a film of "soft" penetration and blurred detail failed to reveal the characteristic shadows. The subsequent examination produced better roentgenograms and a categoric opinion that the patient had microlithiasis. Accessory, but not necessary to the diagnosis, are the facts that there is nearly always a negative history of occupational exposure and of antecedent disease, little or nothing in the way of symptoms or disability, and completely negative physical examination and laboratory tests except in the terminal stage of the disease. This is the situation as of 1956 and it shall probably remain so until we discover the earlier stages of the disease before the calcium salts are deposited in the alveoli, if such be the case. It might therefore seem superfluous to consider differential diagnosis in detail; nevertheless, since miliary processes in the lung are so numerous, more than cursory attention of the problem may be justified.

It is possible to divide and separate the miliary lesions in several ways, on etiologic basis for example, or by size of the lesions, distribution of density or even rapidity of change, but we doubt if anything is gained by so doing. They could be arranged by considering the frequency of their occurrence but that would vary in different parts of the world. They could be grouped according to the severity of symptoms they produced or in many other ways, probably at times with profit. Unfortunately, many of them overlap arbitrary divisions and artificial classifications so that we shall attempt to discuss the more common, confusing processes first and more in detail, keeping the classic appearance of this disease always in mind for contrast.

Miliary tuberculosis is usually given primary consideration when the roentgenogram uncovers a finely mottled diffuse pulmonary process. What we actually see in the roentgenogram, of course, are not the miliary tubercles but coalescent groups of them large enough to cast shadows. The distribution is rarely uniform throughout both lungs but will be lighter in places, coalescent or conglomerate in others, and it usually spares the extreme bases of the lungs. The coalescent nodules in the upper lung areas often are larger than those in the lower lung fields, as if older or more rapidly growing. Frequently there will be evidence of an older lesion, often the source of the hematogenous spread; at times just local fibrosis or coarser nodulation; at other times frank cavitation. In the latter case the interpretation is much easier. Pleural fluid or old pleural scars are common with miliary tuberculosis but rare in case of microlithiasis. Calcification in miliary tuberculosis, when it occurs, is usually limited to small areas where necrosis and caseation have preceded calcium deposition. So far, we have not yet seen extensive diffuse calcification in miliary tuberculosis, but this may occur now that we have the curative drugs. Most, if not all, of the cases reported as healed (calcified) miliary tuberculosis have either been histoplasmosis (calcified) or other fungus disease such as aspergillosis, occasionally pneumoconiosis, hemosiderosis or, perhaps, a case of microlithiasis.

What has been written above for miliary tuberculosis holds true for other pulmonary infections and, particularly, the fungus group which may end up with numerous calcified foci scattered through both lungs, shot-like in appearance, varying from fine bird shot (1–2 mm.) to small bullet (6–7 mm.) size. They are often sharp and distinct in outline, circular or oval in shape, with no adjacent fibrosis or scarring and no

distortion of normal anatomy. There may be and frequently are associated calcium deposits in the hilar and mediastinal lymph nodes and in the spleen, which usually are not involved in microlithiasis. These calcified foci may be numerous (25 to 100) but are not "innumerable" as in microlithiasis, and are individually quite different in size and shape. They occur most commonly in our midwest valley areas, presumably due to Histoplasma capsulatum infection in youth or possibly some other similarly mild fungus infection. As a rule, the host gives no history of previous pulmonary disease or illness.[23,38,40,42,71]

The other infections and the infectious granulomata have no real similarity to the condition under consideration, as they are scattered nodular or coarse poorly-defined areas of exudate, infiltration or atalectasis of only soft tissue density. The same also holds true for the acute bronchiolitis or bronchopneumonias which follow inhalation of toxic gases or volatilized materials. In these cases, of course, the history of acute exposure is important.

More difficult to differentiate are perhaps some of the pneumoconioses. Some of them, like berylliosis, may at first glance resemble microlithiasis until one analyzes the shadows and notes the absence of calcium in each sharply defined nodule. The lesions in berylliosis,[25,54] silicosis,[39,49,51,59,60,62] asbestosis,[45] and bagassosis[44] predominate in the upper halves of the lungs and around the hila, with normal or emphysematous bases. A history of occupational exposure may be obtained in most cases but may be difficult to verify in berylliosis. The most important factor is the absence of innumerable very fine discrete shadows *of calcific density*. When calcification does occur in silicotic lungs it is usually located in and around hilar or mediastinal lymph nodes where it may produce the egg-shell appearance observed most frequently in advanced silicosis, and less frequently in the pulmonary nodules unless tuberculosis is also present.

The lesions due to industrial hazards of welding and of working with powdered tin (tin oxide) and barium[51] present other difficulties in differentiation. Films of the welders' lungs[26,31,58] show numerous small scattered nodular shadows which are sharp in outline but of soft tissue density. They are, in effect, small granulomata around collections of iron oxide and possibly other metals vaporized by the high temperature of the welder's torch. The condition may look serious but in most cases there is no disability and usually there are no discernible symptoms. Calcium deposits do not occur in these granulomas. The deposits may decrease or disappear if the exposure ceases.[26]

The inhalation of finely powdered tin oxide or barium gives rise to very opaque shadows in the lungs which could be mistaken for microlithiasis. In these cases, however, the deposits are of *metallic density* like lead or bismuth, may be more linear and more irregular in size and shape, and have a peculiar distribution, predominantly in the upper two-thirds of the lungs, leaving the bases clear. Very few such cases have been reported from the United States[28,52] but recently an excellent article appeared in the *Journal of the Faculty of Radiologists* by Robertson and Whitaker,[55] reporting 121 cases from the factories in Liverpool. Some of the dense pulmonary shadows were coarse and nodular, others were very fine, but the striking paradox was the absence of symptoms. Tin does not cause fibrosis or scarring in the lungs and thus is similar to siderosis. Chemical analysis of ashed lung in such cases shows as high as 20 per cent of the weight due to tin. This condition is one of the few which might cause real difficulty in differentiation from microlithiasis. Both present innumerable fine, sharply outlined, shadows throughout the lungs, and both are devoid of symptoms. The gross distribution of the shadows, however, is at variance and there is a critical difference in the degree of density, corresponding to the difference between a *calcium density* and a *metallic density*. The distinction can be made if proper roentgenograms are taken and correctly analyzed.

Hemosiderosis has been confused with microlithiasis in several publications and even in textbooks, as noted above. The error has been made in both directions. Microlithiasis has been called hemosiderosis, and cases of hemosiderosis have been included with microlithiasis on scanty histologic similarities, by neglecting characteristic roentgenographic appearances.[17,62]

As the radiologist sees it, pulmonary hemosiderosis occurs in two separate and distinctly different forms. One is the "idiopathic" or acute form occurring in infancy, associated with hemorrhagic or hemolytic tendencies and probably due to a hyperimmune reaction or response. It is recurrent in type and is usually fatal. The lungs show diffuse shadows suggesting edema or hemorrhage which may clear or change rapidly leaving multiple nodular areas behind. Following repeated attacks, the lungs may become progressively damaged, but they never show the minute sharp calcified microliths or, in fact, any calcification at all. An excellent description of the disease appeared recently by Bruwer, *et al.*[22] in the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY & NUCLEAR MEDICINE and by others.[29,34,61] The other form of pulmonary hemosiderosis occurs in patients with mitral stenosis of severe degree (valve area 1.0 sq. cm. or less). Hemosiderin is usually deposited in the minute lymphoid follicles, lymphatics and interstitial tissue, where it is gradually collected until it forms nodules which in some cases simulate miliary tuberculosis or other miliary diseases. These minute nodules may be sharp and clean cut, but they may easily be overlooked. There is no conglomeration of shadows and little or no fibrosis around or between the nodules. They do not calcify but the larger deposits of iron attract calcium and there may result a finely mottled miliary lung with larger calcified foci, variable in size and shape but more like healed histoplasmosis than microlithiasis. In addition, the radiologist will see the enlarged mitral-shaped heart, the dilated left auricle, the calcified mitral valve, and usually the other signs of chronic passive pulmonary congestion such as enlarged pulmonary arteries and Kerley's "B" lines.[30,50,57,60,63]

Sarcoidosis has always been the prototype of extensive pulmonary disease without corresponding symptoms and only as such does it resemble microlithiasis. The enlarged hilar or mediastinal lymph nodes, the soft fluffy pulmonary lesions of variable size and irregular distribution and the clear lung spaces just above the diaphragms should separate most of the cases. The absence of the fine calcified particles is again the critical distinguishing feature. More than half of the cases of pulmonary sarcoidosis occur in Negroes, while in the 45 cases of microlithiasis only one has been identified in a Negro (Case 11). The tuberculin skin test is practically always negative in patients with active sarcoidosis, while it may be positive or negative in microlithiasis without significance. The inverted albumin-globulin ratio often seen in sarcoidosis has not been found in microlithiasis, and sarcoid lesions rarely calcify, never to the extent seen in microlithiasis.[21,46]

Miliary metastases to the lungs, either blood borne or by retrograde lymphatic spread, may at times suggest other miliary conditions, but would never, or at least hardly ever, approach the uniformity in size and in distribution of microlithiasis. In addition, the critical point again is the calcific density of each individual microlith which is so distinctive. Metastases rarely calcify in the lungs or soft tissues with the exception, of course, of bone forming tumors. We formerly taught that this was the only exception to the rule, but in recent years we have seen several cases of nonosseus tumors provoking visible calcification in the abdomen or in the liver. This was first noted in a cystadenocarcinoma of the ovary, later in adenocarcinoma of the pancreas, and more recently also in metastases from adenocarcinoma of the colon.[70] None, however, have produced anything in the lungs which could be confused with

microlithiasis, provided good roentgen technique has been employed.

The same statements hold true in the cases of interstitial organizing pneumonitis and of idiopathic pulmonary fibrosis described by Hamman and Rich.[41] They may each present considerable difficulty in exact identification and they may vary widely from the classic roentgen picture usually ascribed to them, but in no case so far have they approached the fine, discrete, sharp grains-of-sand appearance which characterizes this disease. Many other diffuse pulmonary conditions of rarer occurrence, not truly miliary in appearance or distribution, could be included, such as amyloidosis,[69] eosinophilic granuloma,[32] tropical eosinophilic lung, multiple emboli or thrombi, pulmonary adenomatosis, periarteritis,[27,56] various forms of collagen diseases and other responses to toxic gases or inhaled materials, but none of them really simulate our esoteric disease. Even the miliary nodulation sometimes observed in the rorentgenograms of patients with polycythemia or leukemia fail to approach it. In fact, the only pulmonary condition which may simulate its roentgenographic appearance, in addition to stannosis already mentioned, would be a residue of a lipiodol injection, where the metallic density and fine particle formation might suggest minute calculi or the rare case of diffuse pulmonary emboli. Such a uniform distribution would be highly improbable and yet the remote possibility must be kept in mind.

Some radiologists and "chest physicians" have failed to realize the importance and value of determining the relative density (opacity) of pulmonary lesions. Often they are reported only as either "soft" or "hard." These terms usually refer respectively to exudative or fibrotic processes and not to actual degrees of density. It is much better to search for and record the shadows in terms of standard densities as revealed in the particular film under consideration, for they vary considerably depending upon the technique used. The standards commonly recognized are: (1) air density, (2) fat, (3) soft tissue, (4) calcium, and (5) metallic density. Tooth density lies between bone and metal but need not be considered here. These are the terms describing the *quality* of the opacity and other measures must be used for the degree of density. The usual types of *calcific* densities seen are those in calcified lymph nodes, in arteriosclerotic arteries, healed foci of infection, infarction or necrosis anywhere in the body, some hematomata, many urinary and some biliary calculi and a host of other conditions. Shadows of *metallic* density ordinarily seen in the human body are usually either the result of trauma or related to medication, such as barium, bismuth, iodine, mercury, lead, thorium, and a variety of pills. If, therefore, the critical analysis of the miliary pulmonary shadows in the roentgenogram reveals fine discrete shadows of calcific density uniformly distributed throughout both lungs, it is highly probable that the patient has pulmonary alveolar microlithiasis.

ETIOLOGIC FACTS AND FANCIES

Both the cause and the manner of production of these unusual microliths are unknown. No real clue to the origin, predisposing factors or method of formation can be found in the histories, examinations, laboratory tests, histologic studies or chemical analyses. The only established facts are that this rare condition may occur in young people, with no history or sign of antecedent disease, may lie dormant or latent for 10 to 25 years, and then reveal its presence by slowly increasing pulmonary insufficiency, with the associated changes of cyanosis, clubbing of the digits, polycythemia and finally death either from anoxemia or right heart failure. The majority of cases are discovered accidentally by routine roentgen examination. The only important etiologic clue so far discovered is the fact that the disease occurs in families, which suggests some inherited abnormality or defect in pulmonary metabolism.

Calcium salts are more soluble in acid

media and are more easily precipitated from alkaline solutions. Anything which promotes alkalinity at the alveolar interface where oxygen and carbon dioxide are exchanged would promote the deposition or precipitation of calcium phosphate or carbonate. This ordinarily occurs most commonly in dead or necrotic tissue but can occur in normal tissue under conditions where the solubility product constant $k=(Ca++)3\times(P\equiv)^2$ (normally $36\pm$) is exceeded or where local conditions promote a sudden shift toward the alkaline side. However, the problem of calcium deposition *in tissues* is not germane to the problem, as the deposit is not in tissue but in an exudate or transudate in an otherwise presumably normal alveolus. The microliths are morphologically quite similar to corpora amylacea. Such corpora are considered to be the laminated stagnation products of secretion in the prostate, and of exudate in the lungs.[12] Any number of injuries or insults to the alveolar walls could cause the exudate, but the real problem is to find out what causes the deposit of calcium phosphate and carbonate in the exudate. This is the problem still to be solved.

Another interesting suggestion is that the formation of the microlith is due to an abnormality of carbonic anhydrase which plays an important part in the exchange of oxygen and carbon dioxide and probably also in maintaining normal balances between the extremes of acidity and alkalinity. The enzyme could be deficient, in excess, or abnormal in function in order to disturb the balance.

Given an exudate in the alveoli which under normal conditions would promptly be absorbed, the presence of some organic material normally found only in calcifying tissues or ossifying bone might lead to calcium precipitates. In many microliths there seem to be amorphous nuclei of unknown material, not cellular debris as far as we can tell.[6] Chondroitin-sulphuric acid is such a chelating substance. Elastic fibers from tissue breakdown or collagen may cause the precipitation of hydroxyapatite *in vitro* from unsaturated solutions of calcium and phosphorus,[66] but the mechanism of this reaction is still unknown.

We can be reasonably certain that pulmonary alveolar microlithiasis is not due to an infection by any known bacteria, fungi or yeasts, nor is it due to inflammation in the ordinary sense of the word. It is not the result of occupational exposure, not a tumor, not due to one of the collagen diseases or rheumatic fever, not a sequel of mitral stenosis or any known circulatory disturbance, and not an endocrine abnormality. Neither is it one of the bizarre results of hypervitaminosis D[24] or other vitamin imbalance, nor the sequel to a combination of factors such as produced in nephrocalcinosis.[20,67] There is no abnormal or unusual dietary factor demonstrable. It is not the result of a reaction to any medication or to injections as there is no common ground for such an assumption. The only theories remaining are that it is either a peculiar and unusual response possibly of the hyperimmune type[12] or that it is due to a congenital abnormality of oxygen-carbon dioxide exchange at the alveolar interface.

The (1) long clinical course with pulmonary insufficiency occurring only years after recognition of the lesion roentgenologically, (2) the absence of tissue components in the concretions, (3) the normal appearance of the walls of alveoli containing concretions early in the disease and (4) the lack of a constant relationship to inhaled particulate agents suggest that the components of the concretions are derived from the alveolar capillary circulation and that the ultimate changes in the alveolar walls, which lead to pulmonary insufficiency, are secondary to the prolonged presence of these presumably progressively enlarging concretions. Should this represent the pathogenesis, it would imply that if the process could be halted even though some concretions had already formed, the ultimate pulmonary insufficiency might be averted.

There is at present no known form of

therapy to halt the progress of the disease or to cause remissions in its course. Treatment has been purely supportive and alleviative. Oxygen inhalation and cortisone have given the best relief of symptoms but have had no effect upon the underlying condition. Our greatest hope at present is to discover the cause of this disease and then try to prevent it.

SUMMARY

1. Pulmonary alveolar microlithiasis is not as rare as it was thought to be. We have found 21 acceptable cases reported in the world literature to date. We personally know of 25 more unpublished cases; 23 of them are included in this report.

2. The etiology is unknown. The absence of the usual precipitating factors and the high incidence of familial occurrence strongly suggest an hereditary factor. Thirteen of our 23 new cases occurred in five families.

3. The condition could be due to an inborn error of respiratory metabolism at the alveolar interface, possibly an enzyme fault.

4. The disease may be and usually is asymptomatic for years. It is most often discovered by "routine" chest roentgenography.

5. The roentgenographic appearance is characteristic and pathognomonic. Overexposed or overpenetrated films are necessary to demonstrate the fine sand-like particles spread uniformly throughout both lungs, of *calcific* density, with only slight variation in size, sometimes accentuated along the pleural surfaces, but not conglomerate or coalescent. The total density of the millions of microliths is frequently sufficient to obscure the outlines of the heart and the diaphragm.

6. Once seen it is readily recognized. This again proves that "we see only what we look for; we recognize only what we know."

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VOL. 77, NO. 6

TUBERCULOMAS AND HAMARTOMAS OF THE LUNG*

COMPARATIVE STUDY OF 66 PROVED CASES

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ACCORDING to large surgical statistics[11,20] tuberculomas and hamartomas are the most common solitary, spheroid lesions of the lung in persons under the age of fifty. In the older age groups they are preceded in frequency by malignant tumors. Their incidence will increase with the ever increasing number of photofluorographic surveys and routine roentgenologic examinations of the chest. The aim of this paper is to call attention to certain less commonly observed variations in the roentgen appearance of these lesions as found in a large, surgically proved series. Furthermore, it will be shown under what conditions hamartomas of the lung can be differentiated from tuberculomas on roentgen evidence.

A tuberculoma[5] is a tumor-like granuloma caused by the tubercle bacillus, encapsulated by connective tissue and showing no evidence of surrounding inflammation or spread. It may arise either from a primary or reinfection focus by encapsulation or from a completely blocked tuberculous cavity. Rarely, multiple tuberculomas have been described.[5,16]

Albrecht[1] defined hamartoma as a tumor-like formation in which there is an abnormal arrangement of the normal components of the organ from which it arises. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation or may comprise all three phases. Hamartomas may be found in almost any organ. In the lungs there are two types[10] of hamartomas: (1) the adult type, which is a relatively small lesion, and (2) the infant or newborn type, which is a massive, diffuse process often occupying a lobe or even an entire lung.

Hamartomas of the lung have been variously reported[18] as papilloma, fibroadenoma, mixed tumor, hamartoma chondromatosum, chondroma, adenochondroma and lipochondroma.

MATERIAL AND METHODS

Between 1945 and 1955, there were 43 patients who were operated upon for tuberculomas and 909 patients for other tuberculous lesions of the lungs at the New England Deaconess Hospital, Boston, Massachusetts. During the same eleven-year period, 25 patients underwent resection for pulmonary hamartomas. In four more patients, hamartomas were incidental findings at surgery performed for other reasons.

This study is based on 41 cases of tuberculoma and 25 cases of hamartoma in which the preoperative roentgenograms were available for review. The roentgenograms were usually taken in the postero-anterior and lateral or oblique views. Laminagrams of 6 patients were also available in the tuberculoma group. A few patients also had bronchograms. In each case the roentgen evidence was correlated with the clinical and histologic findings.

RESULTS

We observed 52 tuberculomas in the lungs of 41 patients, 21 men and 20 women, all white, aged twenty-six to seventy-four, with an average age of 46.7 years. Their age distribution is recorded in Table 1. While 33 patients had a single lesion, 6 patients had two, 1 patient three (Fig. 1) and 1 patient had four tuberculomas (Fig. 2), as demonstrated on roentgenograms taken prior to surgery. Tubercle bacilli were found in the sputum of 3 and in the excised tuberculoma of 8 patients. These

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TABLE I

AGE DISTRIBUTION OF PATIENTS WITH PULMONARY TUBERCULOMAS AND HAMARTOMAS

Age (yrs.)	21–30	31–40	41–50	51–60	61–70	71–80	Total
Cases of tuberculoma	7 (17 per cent)	8 (19.5 per cent)	9 (21.9 per cent)	12 (29.2 per cent)	4 (9.7 per cent)	1 (2.4 per cent)	41
Cases of hamartoma	—	1 (4 per cent)	6 (24 per cent)	12 (48 per cent)	5 (20 per cent)	1 (4 per cent)	25

patients will be referred to as the "positive" group.

All tuberculomas in this series were well-circumscribed and subpleurally located. On the posteroanterior roentgenogram they appeared in the lateral lung fields in 29 patients and close to the hilus in 12. Their lobar distribution is recorded in Table II. No perifocal reaction was seen. On the other hand, in 9 patients, 7 of whom were "positive," the drainage channels to the hilus were accentuated (Fig. 3)—a characteristic not seen with hamartomas. In only 1 patient was the tuberculoma part of an advanced pulmonary tuberculosis. So-called "satellites" or daughter tuberculomas (Fig. 4) were seen on the roentgenograms in only 2 patients while the surgical specimen revealed them more often. On the other hand, translucent areas (Fig. 3) within the tuberculoma were seen in 14 patients (34.1 per cent); in 2 instances they were also shown on laminagrams, although the excised and fixed specimen revealed no cavitation. In 1 case, the routine posteroanterior roentgenogram showed a definite "umbilication" which, at the pathologic examination, turned out to be due to the partially superimposed shadow of two tuberculomas. No laminagrams were taken in this case. Definite lamination on routine films was seen only twice.

FIG. 1. Three tuberculomas in the left lower lobe of a recently discovered diabetic. Laminagram taken at 10 cm. shows a calcific core in the upper and lower nodule.

In the posteroanterior projection the tuberculomas appeared oval in 21 instances and round in 27, their size ranging from 0.5 by 0.5 cm. to 3.5 by 5.0 cm. In the "positive" group the size ranged from 1.0 by 2.0 cm. to 3.5 by 5.0 cm., thus tending to be somewhat larger than in the negative group.

In 23 patients (56 per cent), the tuberculoma was clinically silent and was discovered on routine or survey chest films. In 14 patients (34.1 per cent), the history and the symptoms were referable to tuberculosis. In only 4 patients (9.9 per cent) were the history, symptoms and the physical signs suggestive of tuberculosis. Of the 11 "positive" patients 3 were asymptomatic and were discovered by routine roentgenograms, 5 had a history and symptoms suggestive of tuberculosis while 3 had the history, symptoms and physical signs of pulmonary tuberculosis. Of the 8 patients who had more than one tuberculoma, 3 had

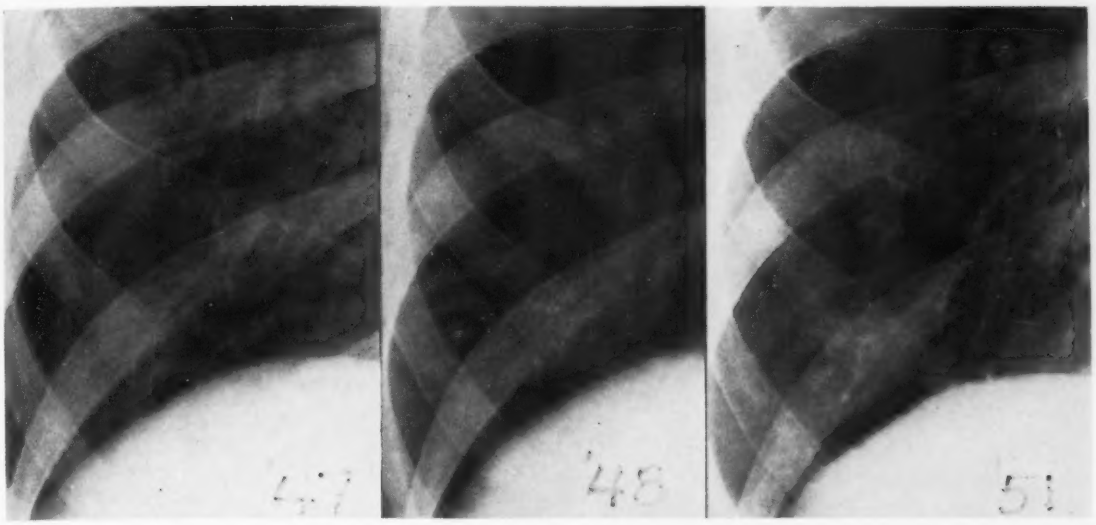

Fig. 2. Case 1. Female, aged thirty-nine, had right mastectomy in 1946. She was exposed to tuberculosis about the same time. Right lower lung field appeared clear in 1947, showed one nodule a year later and three in 1951.

a suggestive history, 4 had mild symptoms and none had physical signs referable to pulmonary disease. It is noteworthy that while there was only 1 diabetic among 25 patients (4 per cent) with pulmonary hamartoma, there were 8 diabetics among 41 patients with tuberculoma (19.5 per cent), 4 of them being "positive." Furthermore, 3 tuberculoma patients, 1 "positive" and 2 negative, had mitral stenosis.

Calcification was seen in the tuberculomas of 11 patients (26.8 per cent); in only 1 of them were laminagrams taken which revealed calcification not seen on the routine films. The calcification was diffuse in 1 case, had the appearance of a round central core in 1 instance, while in 9 cases small flecks of calcium were scattered without a definite pattern. Only 1 of the "positive" cases had demonstrable calcium.

The tuberculomas were removed by wedge resection in 26 patients, by segmental resection in 10, by lobectomy in 4 and by pneumonectomy in 1. The last patient had advanced tuberculosis. Lobectomies were performed either because of technical difficulties or because the gross appearance of the nodule suggested malignant neoplasm.

Documented chronologic data on the development and course of tuberculomas were available in 2 patients of this series and in one additional patient (Case III) who did not have surgery but was observed during the same period of time and presented the typical complication of tuberculomas.

REPORT OF CASES

Case 1. B.B., a thirty-nine year old white nurse, had chest roentgenograms taken six years previously because of exposure to tuber-

Table II

LOBAR DISTRIBUTION OF LUNG TUBERCULOMAS AND HAMARTOMAS

	Right Upper Lobe	Right Middle Lobe	Right Lower Lobe	Left Upper Lobe	Left Lower Lobe	Total
Number of tuberculomas	4	1	12	18	17	52
Number of hamartomas	—	3	3	11	8	25

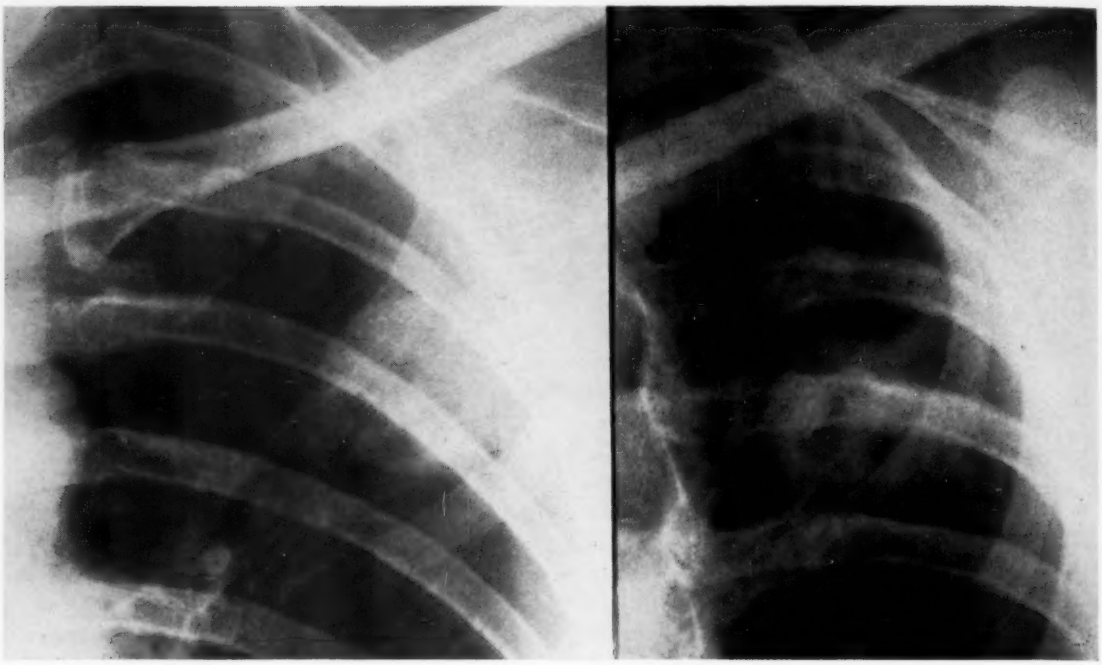

FIG. 3. Tuberculoma in the left upper lobe of a diabetic. Translucent areas in the tuberculoma and drainage channels to the hilus are well seen.

culosis. These roentgenograms were said to be negative. About the same time, she had a right radical mastectomy for cancer. Two years later one round nodule appeared in the right lung. On admission, chest roentgenogram showed four nodules (Fig. 2). She was well clinically and the physical examination was negative. Exploration revealed seven nodules, 1 to 2 cm. in diameter, scattered over all three lobes on the right. Right lower lobectomy and wedge resection of the middle and upper lobe were performed. The nodules proved to be tuberculomas histologically though no acid fast bacilli were found. A lobular lymph node also showed tuberculosis.

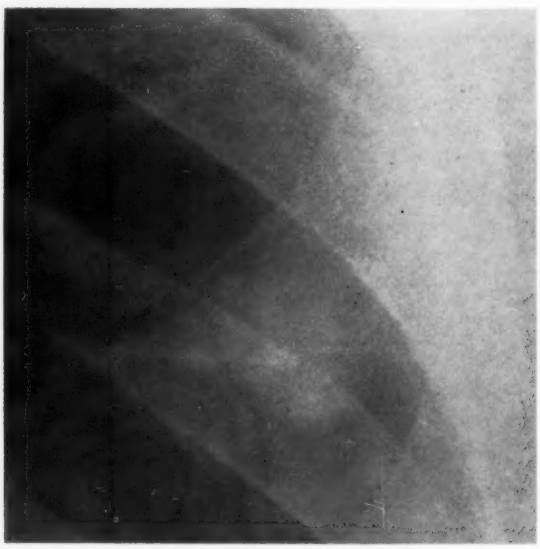

FIG. 4. Tuberculoma in the lingula with characteristic "satellites" around it.

CASE II. M.B., a twenty-six year old white housewife, was exposed to tuberculosis eight years previously. A "growing nodule" was noted about four years later in her right lung. Pneumothorax and pneumoperitoneum had failed. Two and one half years prior to her present admission roentgenograms of the chest revealed a smooth, homogeneous nodule, 1.5 cm. in diameter, in the left upper lobe and three similar nodules in the right upper lobe. First, the nodules on the right were excised. Six months later the nodule on the left side, which had increased from 1.5 to 3 cm., was resected. Histologically, the nodules were tuberculomas.

On admission, the patient was clinically well and symptom free. Physical examination was negative except for auscultatory findings

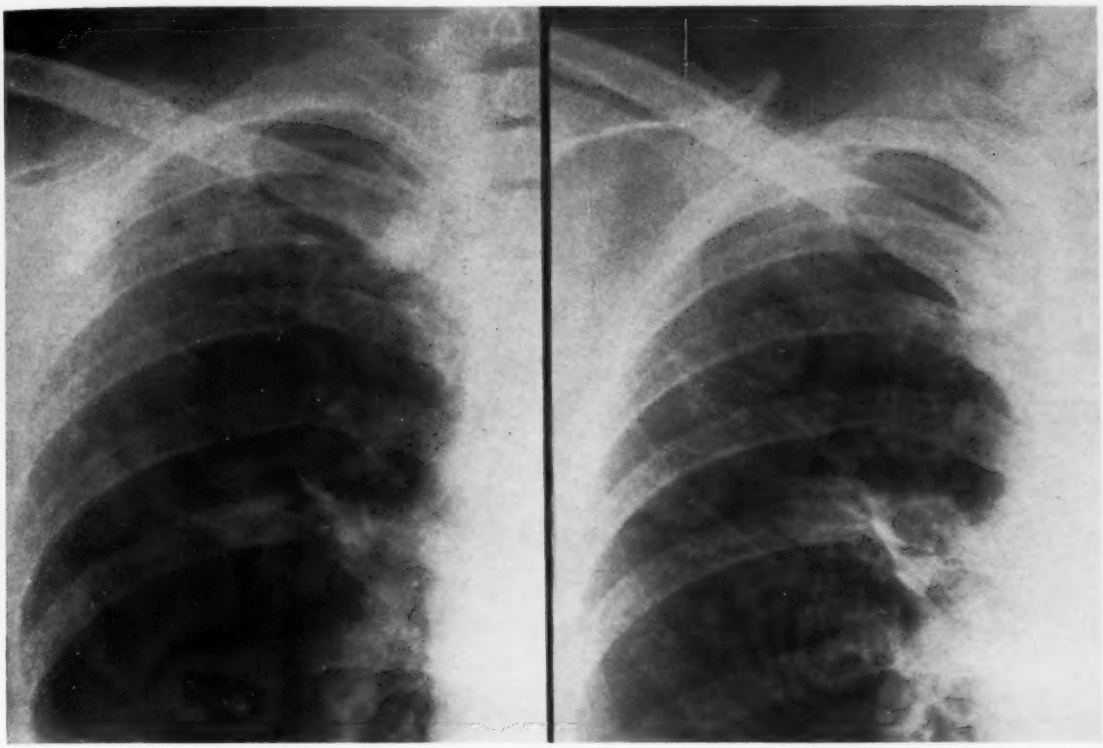

Fig. 5. Case III. Tuberculous spread from a tuberculoma, eighteen months after its discovery.

consistent with mitral stenosis. Chest roentgenograms, taken twenty-three months after her second operation, revealed two round shadows beneath the anterior end of the second rib, measuring 1.8 and 3 cm. in diameter, respectively. The nodules, found in the anterior segment of the right upper lobe and in the superior segment of the right lower lobe, were excised. Histologic examination showed tuberculomas containing acid-fast organisms.

Case III. A.A., a sixty-three year old white housewife, had had diabetes for twenty-one years. A round nodule in the right upper lobe, 2 cm. in diameter, was discovered on routine roentgen examination. It was unchanged one year later but broke down and spread eighteen months after its discovery (Fig. 5).

Hamartomas were found in 14 men and 11 women, all white, aged thirty-eight to seventy-one, with an average age of 55.1 years. The age distribution of the patients is seen in Table I.

All hamartomas in this series were solitary, sharply delineated, and without any roentgenographic signs of perifocal reaction (Fig. 6). In 20 patients they were situated within the lung parenchyma and close to the pleural surface. Their lobar distribution is seen in Table II. In the remaining 5 patients the hamartomas were found in a major bronchus, three times in the left upper lobe and once each in the left lower and right middle lobe.

The hamartomas of the parenchyma appeared on the posteroanterior roentgenograms peripherally in 15 cases and more centrally in 5 cases. They were ovoid in 11 and spherical in 9 instances. The nodules measured from 0.5 to 4.5 cm. in diameter. Increase in size of the nodule was noticed in 1 patient (Fig. 7). Calcification was definitely present in the roentgenograms of 3 patients (15 per cent). Translucent areas of 2 to 3 mm. in diameter were seen in two nodules (10 per cent).

The intrabronchial hamartomas caused atelectasis of the respective pulmonary segment (Fig. 8). The mass causing the obstruction was not visible on the plain roent-

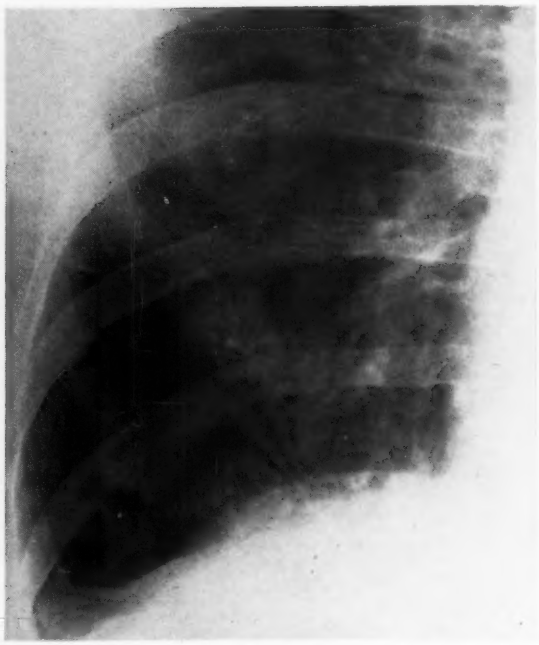

FIG. 6. Hamartoma in the right middle lobe, sharply delineated, without perifocal reaction, and with calcification.

genograms. Three of the 5 patients with such obstruction were bronchoscoped prior to surgery. In 2 the hamartoma was seen, in the third bronchoscopy was unsuccessful but the subsequent bronchogram (Fig. 9) revealed the hamartoma as a mass protruding into the lumen of the lower lobe bronchus.

The intrabronchial hamartomas were accompanied by clinical symptoms and signs such as cough and expectoration in 4 patients and hemoptysis in 1. The parenchymal hamartomas, on the other hand, were clinically silent and were detected during survey or routine roentgenologic examinations.

The parenchymal hamartomas were removed by wedge or segmental resection in 18 patients, while lobectomy was done in 2 because the frozen sections seemed to indicate malignant neoplasm. The intrabronchial hamartomas necessitated lobectomy in 3 patients and pneumonectomy in 2.

DISCUSSION

Mycobacterium tuberculosis was found in 11 of our tuberculoma patients. Probably, by culturing the resected specimens the incidence would have been higher. But even with complete bacteriologic studies, including cultures of the removed granuloma, as done by Good, *et al.*[7] on 53 granulomas, the causative agent could not be identified in their series in 42; Myco-

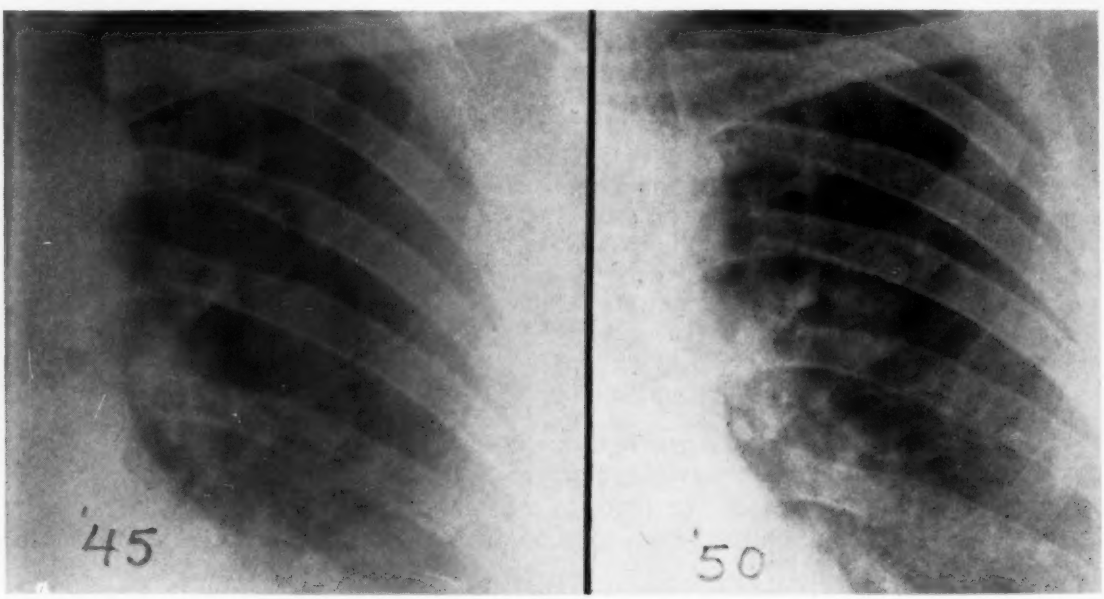

FIG. 7. Hamartoma, showing definite increase over a five-year priod.

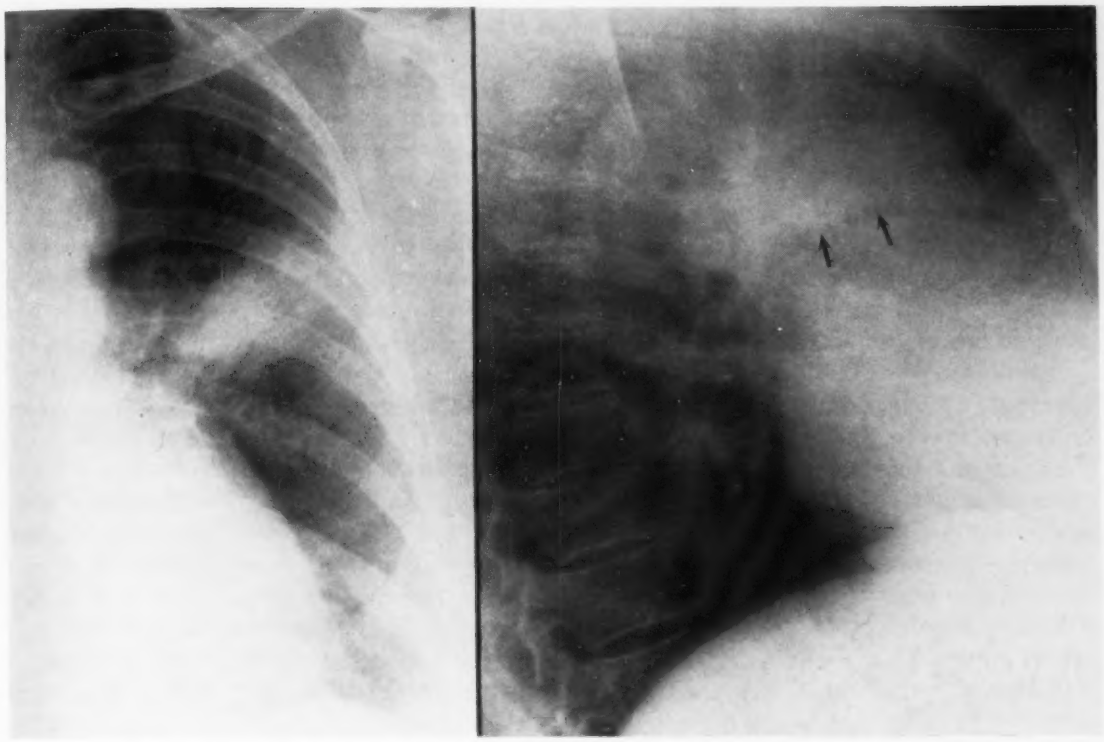

FIG. 8. Partial atelectasis of the left upper lobe due to an intrabronchial hamartoma.

bacterium tuberculosis was recovered in 7, Coccidiodes immitis in 3 and Brucella suis in 1 case. On the other hand, the close similarity in roentgen appearance, clinical course and surgical results, as well as the statistical prevalence of tuberculous granulomas, seem to warrant calling the granlomas of our series, at least for practical purposes, tuberculomas. This was also the working diagnosis in all cases where a granuloma was suspected preoperatively.

Certain phases of the natural history of a tuberculoma are well illustrated by our cases. In Cases I and II the first tuberculomas appeared about two to four years after exposure. They first remained clinically silent. It took one and one half to four years for the development of several tuberculomas in the same patient, six months to double the size of one tuberculoma, and twenty-three months for recurrence in the same and in an adjacent lobe following surgery for preceding tuberculomas. How often recurrences took place in our entire

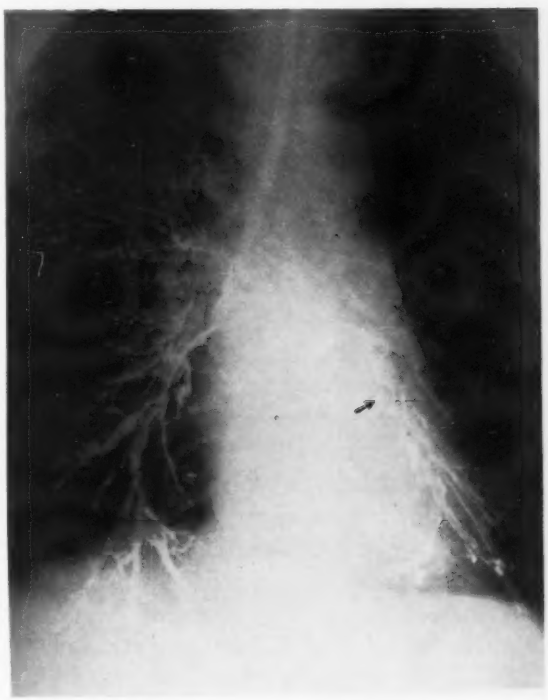

FIG. 9. Hamartoma bulging into the left lobe bronchus.

group is not known since we did not attempt follow-up investigations. Nor did we find any references in the literature pertaining to recurrence of tuberculomas.

The tuberculoma probably represents the most benign form of tuberculosis and in its early stages is rarely if ever accompanied by advanced tuberculosis. Such occurred only once among our 41 patients. This is perhaps due to the fact that with a few exceptions the patients in this series had their tuberculomas removed soon after they were discovered. The benignity of tuberculomas, however, is relative and lasts only until their capsule breaks down, or until the cavity which precedes some of them reopens. They then discharge their contents into the bronchial tree as occurred in 3 of our patients.

When will a pulmonary tuberculoma break down? This varies greatly from individual to individual. Rüttimann and Suter,[16] in a follow-up study of 77 patients with 87 pulmonary tuberculomas, followed over one to ten years, found that 40 tuberculomas (46 per cent) did break down. Although this occurred mostly within three to twelve months following their discovery, in some instances reactivation set in as late as nine years. Thus, to label tuberculomas "time bombs" seems quite appropriate. That tuberculomas do not remain unchanged indefinitely is probably the reason why they are rarely found incidentally at autopsies.[15,16]

Many tuberculomas have in common with hamartomas and other solitary nodular densities of the lung the average size, shape, sharp border and subpleural location. If they contain calcium, they are readily distinguished from all primary carcinomas and from almost all metastatic tumors. If laminagrams had been taken more often, probably the incidence of calcification in our series (26.8 per cent) would be higher. Black and Ackerman,[2] and Grenville-Mathers[8] found an even lower incidence of calcification. It is noteworthy, however, that calcification was seen in only 1 patient of the "positive" group. Thus, the presence of even small flecks of calcium seems to indicate that the process is relatively inactive.

Radiolucent areas, usually a few millimeters in diameter, are a rather common and characteristic feature of tuberculomas. They were present in 14 of our patients (34.1 per cent). That such radiolucent areas were not always demonstrated by the pathologist is perhaps due to shrinkage of the tissue during fixation. The areas are frequently of a stellate shape, and probably should not be thought of as "cavities" except when they are relatively large or when they show a fluid level, thus indicating bronchial communication.

So-called "satellites," or daughter nodules, are characteristic of tuberculomas. They were encountered more often in the surgical specimen than seen roentgenologically. The discrepancy is probably due to their small size. Here again, laminagraphy might help in discovering these nodules not seen ordinarily.

Of great importance, when present, is the accentuation of the lymph channels to the hilus which was seen in 2 negative and 7 "positive" patients.

Pulmonary hamartomas are histologically benign. In a review of more than 100 cases collected from the literature, Carlsen and Kiaer[4] did not find a single proved case of a malignant, metastasizing hamartoma. Rarely, hamartomas will grow slowly as in 1 of our patients (Fig. 3). The incidence rate of growing hamartomas would probably be higher if serial roentgenograms had been available as in 10 patients of Weisel, *et al.*,[19] in whom the hamartomas were definitely enlarging and in 9 patients gave the clinical impression of bronchogenic carcinoma. But even these enlarging hamartomas have shown no lymph node metastases, no multiplicity nor recurrence.

Parenchymal hamartomas are readily discovered roentgenographically if they are at least 0.5 cm. in diameter, not obscured by other lung lesions, and if films are taken in at least two positions.

In our series of hamartomas there was only a slight preponderance of men over women. Others found the ratio of men to

Table III

DIFFERENTIATION OF PULMONARY TUBERCULOMAS AND HAMARTOMAS

	Tuberculoma	Hamartoma
1. Age under forty	common (36.5 per cent)	uncommon (4 per cent)
2. Prominence of strands from the lesions to the hilus	relatively common (21.9 per cent)	not observed
3. Multiple lesions	relatively common (19.5 per cent)	not observed
4. Daughter nodes ("satellites")	occasional (4.8 per cent)	not observed
5. Translucent areas	relatively common (34.1 per cent)	occasional (10 per cent)
6. Calcification	rare in "positive" cases, relatively common in negative cases (26.8 per cent)	relatively common (15 per cent)

women 2.5:1 to 4:1.[3,12–14,18] The age distribution was significant only inasmuch as there was only 1 patient under forty years of age. Other authors have observed a similar age incidence. The lobar distribution showed a preference for the left side. Others have found either no preponderance of a certain side[9] or one of the right lung.[3,13,14]

The size, shape, sharp delineation and homogeneous appearance on the roentgenograms are not exclusive characteristics of hamartomas. Tuberculomas, primary carcinomas of the peripheral type, metastatic tumors, chronic lung abscesses, infected cysts and infarcts may have the same appearance. Nor is calcification of much diagnostic help. Ever since the roentgenographic studies of Hickey and Simpson[9] in 1926, the tendency of these tumors to calcify has been stressed. However, more recent reports[13,17] have pointed out that calcification may not be demonstrated even by laminagraphy in one third to two thirds of the cases. We found calcification in 15 per cent of our cases on routine films where it is often difficult to determine whether a calcific density is inside of or just superimposed on a hamartoma. Therefore, we considered calcium to be present in a hamartoma, as well as in a tuberculoma, only if it was seen within the mass in at least two views. Admittedly, laminagraphy would probably have increased our chances to observe calcification.

Hamartomas may be present in the lung when there is malignancy elsewhere in the body, including the lungs. We observed 4 such cases: In 2 instances the same lung lobe harbored a bronchogenic carcinoma and a hamartoma; in the third case a hamartoma was found in the same lobe with a metastatic fibrosarcoma, while in the fourth case carcinoma of the esophagus was accompanied by a hamartoma in the left lower lobe. In 2 instances the hamartomas measured less than 0.5 cm. in the surgical specimen and were not seen on the preoperative roentgenograms. In the other 2 cases, the preoperative roentgenograms were not available for review. A similar case was reported by Davidson and Stern[6] who observed a hamartoma simulating ipsilateral metastasis of an epidermal carcinoma of the left upper lobe. Thus, in a cancer patient, not every lung nodule means metastasis, as shown in Case 1.

Table III summarizes the main features in the roentgen appearance of pulmonary tuberculomas and parenchymatous hamartomas, and indicates their points of difference. More frequent use of laminagraphy, plus careful correlation of the history and of bacteriologic study of the sputum may aid in further differentiation of these lesions.

SUMMARY

The roentgen characteristics of 52 pulmonary tuberculomas occurring in 41 patients and 25 pulmonary hamartomas (20 parenchymal and 5 intrabronchial) are presented and correlated with the clinical, surgical, and histologic findings. Certain

phases of the natural history of tuberculomas, as demonstrated by single and multiple lesions and seen in serial roentgenograms, are described. It was found that tuberculomas possess some characteristics which, if present, may aid in their roentgen differentiation.

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CALCIFICATION IN SOLITARY NODULES OF THE LUNG*

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THE solitary circumscribed nodular lesion in the lung, the so-called coin lesion, has become more important diagnostically to physicians in recent years because of the roentgenograms of the thorax obtained in mass surveys and in conjunction with routine physical examinations. The discovery of such a silent lesion immediately raises the question of its pathologic nature. Is the lesion benign or malignant? What diagnostic procedures should be carried out? How reliable are they, and to what extent should they be pursued? Should exploratory thoracotomy be done in all cases so that miscroscopic examination of the tissue can be made?

A study of 156 cases of solitary nodular lesions removed surgically at the Mayo Clinic during the period January 1, 1940, to June 30, 1951, was made by Good, Hood and McDonald.[8] They concluded that the the only reasonably reliable sign of benignancy was the demonstration of calcification by roentgenologic study. Because of the significance of their observation, a further study of calcification of such lesions seemed warranted.

LITERATURE AND DISCUSSION OF THE PROBLEM

The variation of incidence of malignancy in asymptomatic solitary nodular lesions from 17 to 78 per cent in the published series is misleading. The factor of age and classification must certainly be taken into account. The lowest percentage (17 per cent), reported by Effler and co-workers,[6] was obtained from study of a group of patients who were young men in military service. The majority of patients studied by other authors were in the cancer age. Good, Hood and McDonald[8] found that the incidence of malignant lesions was 25 per cent for the fourth decade, 27 per cent for the fifth decade, 40 per cent for the sixth decade, and 54 per cent for the seventh decade. They pointed out that often these lesions are removed because of the possibility of malignancy and that, because of the tendency of physicians to observe lesions in younger patients by means of serial roentgenograms, the average age of patients included in most reports is that age in which malignant lesions are commonly found. O'Brien and his co-workers[13] stated that age should not be considered a factor in diagnosis, since they found carcinoma of the lung in young individuals.

The classification of tumors also influences the statistics to some extent. The inclusion of adenomas with malignant lesions raises the percentage of malignancy. These properly should be included, for, as McBurney, Kirklin and Woolner[12] have pointed out, metastasis has been found to be present in about 10 per cent of the cases of adenoma of the lung reported in the literature.

It seems justifiable to include metastatic lesions with the primary pulmonary lesions

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for statistical purposes, for in many instances the presence of a solitary asymptomatic nodular lesion is the only sign of a primary lesion situated elsewhere in the body, and its removal had led to the correct diagnosis.

Even though statistical discrepancies occur, it is acknowledged that the isolated solitary nodule in the lung is malignant in a sufficiently high percentage of cases to justify surgical exploration unless the evidence in favor of the lesion's being benign is overwhelming.

The presence of calcification, as evidenced by roentgenologic studies, has been interpreted by several authors[1,2,4] to mean that the lesion is benign. On the other hand, O'Brien, Tuttle and Ferkaney[13] stated that "carcinomas can arise about a Gohn tubercle and old long standing pyogenic abscesses of the lung may contain calcium in their centers and in their walls." This fact has been pointed out by other authors, notably Woodruff and Nahas,[16] who suggested that calcified tracheobronchial lymph nodes might make an area in the lung more susceptible to the development of a carcinoma.

Thomsen and Chrom[14] reviewed the literature on the problem of cancer versus tuberculosis and concluded that the finding of a tumor arising from a tuberculous lesion is probably coincidental. Other authors also have pointed out that a primary or metastatic tumor may be seen in close association with, or to have engulfed, an old calcified inflammatory focus. That malignant tumors also may undergo necrosis and calcify is a well-established fact.[3,11,15]

That benign lesions calcify was pointed out in an early study by Graham and Singer[9] at a time when nodular lesions in the lung were first being attacked surgically. They described the removal of three benign tumors which were associated with cough and expectoration; two of these tumors showed evidence of dense calcification. The calcification of one was described as being laid down between concentric rings of fibrous tissue. All were bacteriologically negative.

Good, Clagett and Weed[7] in a study of 65 cases of pulmonary granuloma, removed surgically at the Mayo Clinic, found preoperative roentgenographic evidence of calcification in 13. In five additional cases evidence of calcification was found in the roentgenogram after pathologic examination of the specimen. A characteristic layering of the tissue in concentric rings was observed in 13 of the pathologic specimens, five of which showed roentgenologic evidence of calcification preoperatively. This supports the work of Graham and Singer.[9] Good and associates[8] reported that 20 of 65 granulomas in their series had a laminated appearance roentgenologically. They described this characteristic by saying that "the shadow of the mass looks as if the tissue had been laid down in layers, with some of the layers being more dense than others." They found this characteristic only in the granulomas and believed this feature to be a mark of calcification.

Lemon and Good[10] studied 17 hamartomas removed surgically at the Mayo Clinic and found calcification in 11 (64.7 per cent). They reported that only two of these lesions gave roentgenologic evidence of the popcorn appearance described by other authors as typical of hamartoma. They pointed out that the preoperative roentgenograms in 11 of the 17 cases studied gave no evidence or insufficient evidence that calcification was present within the tumor mass.

Bloch[5] stated that the term "calcification" as used in roentgenologic diagnosis is arbitrary. Absence of a certain degree of density in any roentgenographic shadow does not rule out the presence of fairly abundant calcification. He also showed experimentally that in order to produce the degree of density customarily attributed to calcification, a lesion had to be packed with calcium.

Many authors have expressed the view that some form of body-section roentgenography, such as laminagraphy, should be

employed as part of the examination whenever evidence of calcification of a solitary mass is lacking in plain, stereoscopic, and Bucky roentgenograms of the thorax.

PURPOSE, MATERIAL AND METHODS USED IN THE PRESENT STUDY

This present study was undertaken to determine whether calcification may be present in a greater percentage of the solitary nodular lesions of the lung than has been detected on the usual preoperative stereoscopic and lateral roentgenograms, and to learn whether special studies, as by laminagraphy, would increase the incidence of detection of calcification in these lesions.

Material Studied. In 149 of the 156 cases reported by Good, Hood and McDonald,[8] pathologic specimens were available for further study, the specimens in the other seven cases having been destroyed by prior pathologic sectioning or bacteriologic examination. To this group of 149 cases we added cases in which pulmonary operations were performed at the Mayo Clinic for an isolated solitary nodule or circumscribed mass from July 1, 1951 to December 30, 1952. There were 65 of these cases with 58 specimens available for study. Selection was according to the method used for the initial cases:[8] A mass appeared to be in the substance of the lung and was the only roentgenologic evidence of significant pulmonary disease. The mass was not associated with the picture of obstruction of a bronchus and showed no evidence of cavitation. A total of 207 specimens removed at operation in 207 cases were available for this study together with the preoperative roentgenograms of the thorax in the 207 cases.

Roentgenograms were made of each of the 207 specimens without intensifying screens. The technique was modified to fit the thickness of the specimen. In all the lesions showing calcification, the mass was carefully dissected away from its surrounding lung substance, preserving any capsule present with the lesion. These specimens were washed carefully under a stream of water to remove dirt and oil from their surfaces. Roentgenograms of the enucleated and washed specimens were made using the same technique as before. The calcified areas were cut from the specimens and sections for microscopic study were made from all the blocks sectioned and stained with hematoxylin and eosin. To study the type of calcification present, the sections were stained for calcium after the method of von Kossa.

The case reports were reviewed for pertinent data.

REPORT OF ILLUSTRATIVE CASES

Five cases will be reported briefly to show the type of lesion and the operative findings.

Case 1 (Fig. 1 and 2). A fifty-nine year old white man came to the clinic because of a nodular lesion in the thorax picked up on a routine examination in October, 1952. The patient had an attack of flu followed by a productive cough in September, 1952, but the cough and expectorations had subsided by the time he was examined several weeks later. Stereoscopic posteroanterior and lateral roentgenograms of the thorax (Fig. 1*a*) revealed a nodule, 3 cm. in diameter, in the right lung field containing central calcification. Laminagrams (Fig. 1*b*) revealed minimal laminated calcification and the diagnosis of granuloma was made. Tests with second-strength PPD tuberculin gave 2+ positive reactions. Four specimens of sputum were negative cytologically. A segmental, V-shaped resection of the lung was performed. The pathologic diagnosis was laminated calcified granuloma (Fig. 2). Cultures of the removed specimen were negative for tuberculosis, Brucella, and fungi.

Case 11 (Fig. 3 and 4). A fifty-five year old white woman was found to have a circumscribed mass containing calcium in its center in the right lower part of the lung field during routine examination at the clinic in April, 1944 (Fig. 3*a*). The lesion was believed to be a hamartoma or granuloma. Tests with PPD tuberculin second strength gave 3+ positive reactions. Sputum smears were negative for acid-fast bacilli. At operation the lesion was found to arise from the superior margin of the

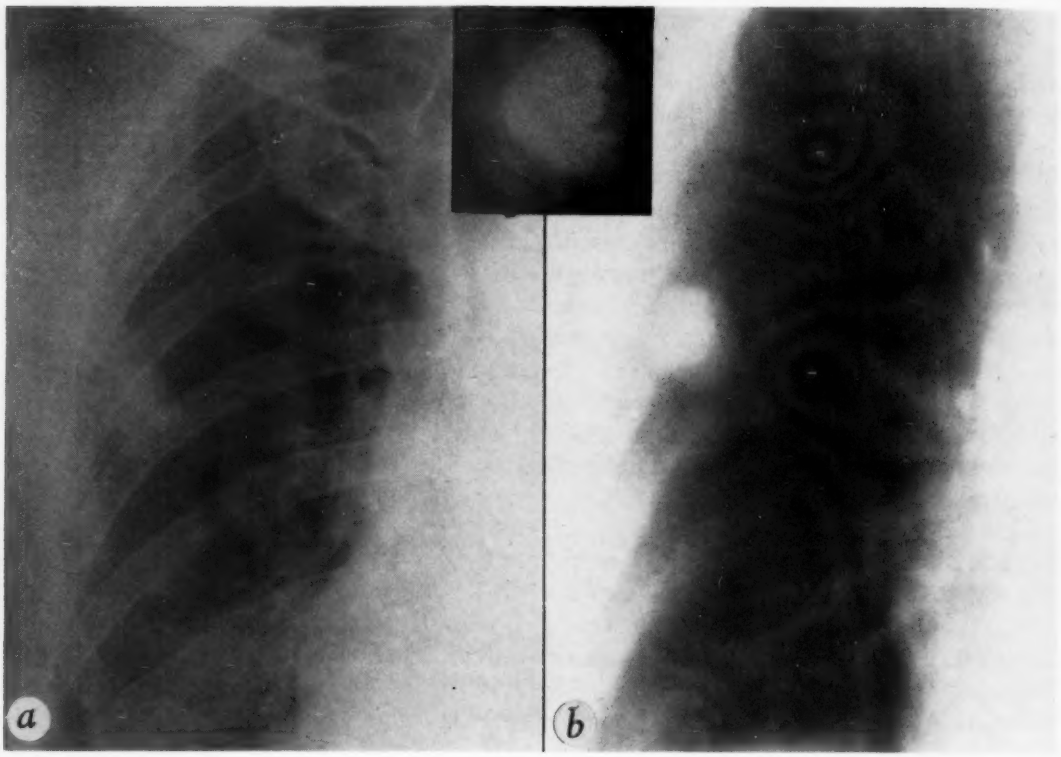


FIG. 1. Case I. *a.* Preoperative roentgenogram revealed a 3 cm. nodular lesion in the right lateral lung field containing central calcification. *b.* Laminagram showed the lesion to have a laminated appearance. *Inset.* A roentgenogram of the excised nodular lesion demonstrates the laminated appearance of the calcified lesion.

right lower lobe and to extend into the fissure between the lower and middle lobes. Local excision of the mass was done. Pathologic examination (Fig. 4) revealed a hamartoma containing bone, cartilage, fat and glands. The patient made an uneventful recovery. Roentgenograms

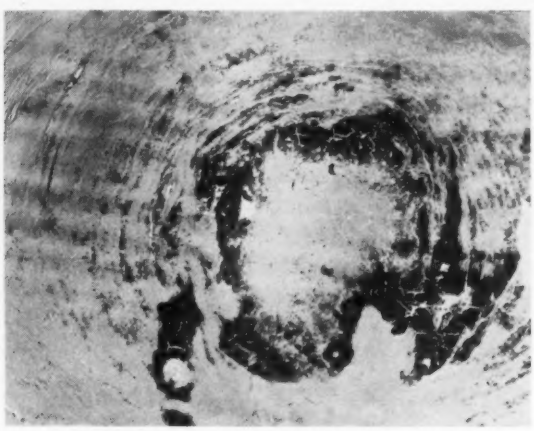


FIG. 2. Case I. Granuloma with the calcium laid down in concentric layers (von Kossa stain; ×4).

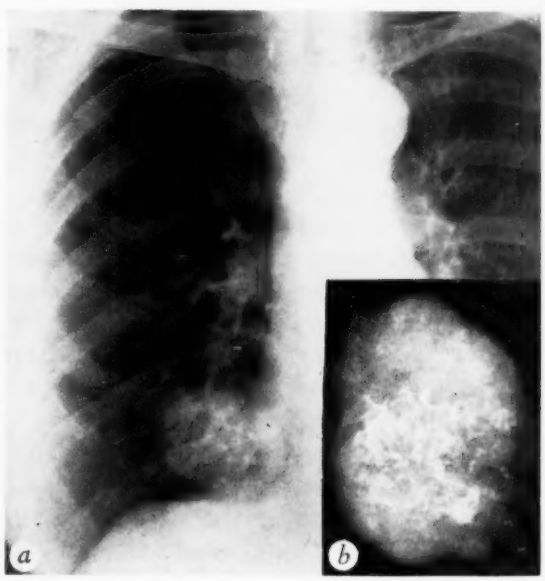
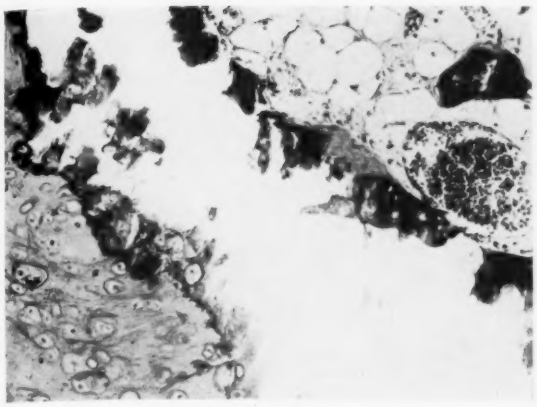


FIG. 3. Case II. *a.* Preoperative posteroanterior roentgenogram revealed a well-circumscribed lesion containing calcium. *b.* Roentgenogram of the pathologic specimen showed the popcorn type of calcification throughout the lesion.



of the specimen showed a popcorn type calcification in the osseous elements, characteristic of hamartoma.

Case III (Fig. 5). A fifty-six year old white man had a roentgenogram of the thorax taken in August, 1951, in the course of a medical work-up because of fatigability. This disclosed a well-circumscribed mass in the lower part of the left lung. Repeated roentgenograms on

Fig. 4. Case II. Calcification present in the osseous elements of the hamartoma (von Kossa stain; ×70).

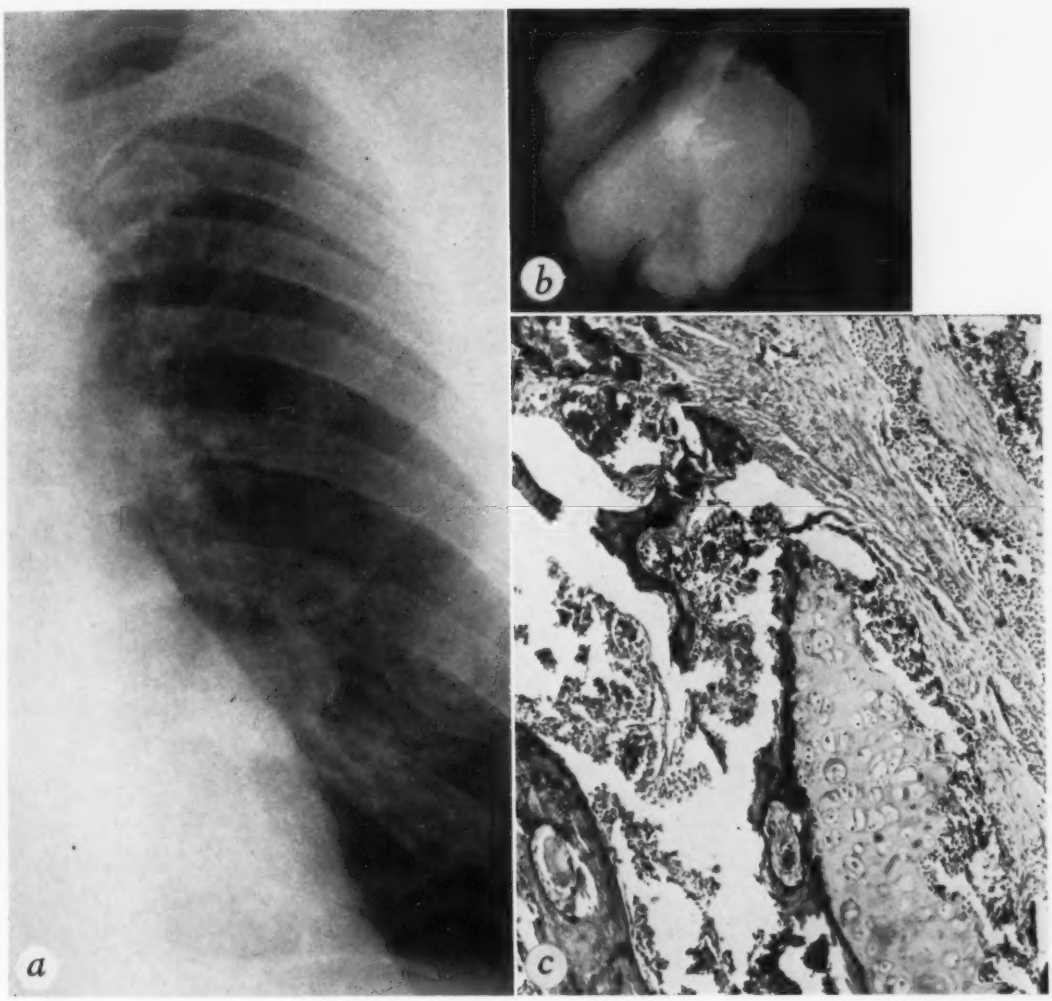


Fig. 5. Case III. *a*. Preoperative roentgenogram of a fifty-six year old white man revealed a well-circumscribed mass below the left hilus. *b*. The excised lesion in *a* shows roentgenographically an area of calcification eccentrically located with the mass. *c*. A section of tissue through the calcified area shown in *b* shows that the calcium is laid down in ossified bronchial cartilage which has been surrounded by an adenoma (von Kossa; ×75).

coming to the clinic in December, 1951, revealed the mass to be located below the left hilus (Fig. 5*a*). Laminagrams did not demonstrate calcification. The history indicated an exposure to tuberculosis at the age of eight years. Tests with PPD tuberculin were positive 3+. Results of all other laboratory examinations, including cytologic studies, were negative. Bronchoscopy revealed only chronic bronchitis. At operation the mass was easily located and biopsy was carried out. Because of the nature of the tumor, segmental resection of the basilar division of the left lower lobe was performed. Pathologic examination revealed an adenoma (carcinoid type) measuring 4 by 4 by 3 cm., with no involvement of the lymph nodes. The patient made an uneventful recovery. Roentgenograms of the specimen (Fig. 5*b*) disclosed an eccentric area of calcification, and microscopic section stained after the method of von Kossa showed that the calcium was laid down in an ossified bronchial cartilage which has been surrounded by the tumor mass.

CASE IV (Fig. 6). A white man, aged sixty-nine years, was discovered to have a lesion about 1 cm. in diameter in the left mid-lung field on a routine roentgenogram of the thorax in the fall of 1948. A follow-up roentgenogram in January, 1951, showed that the lesion had grown to the size of a quarter (Fig. 6*a*). The patient had had cough with some expectoration

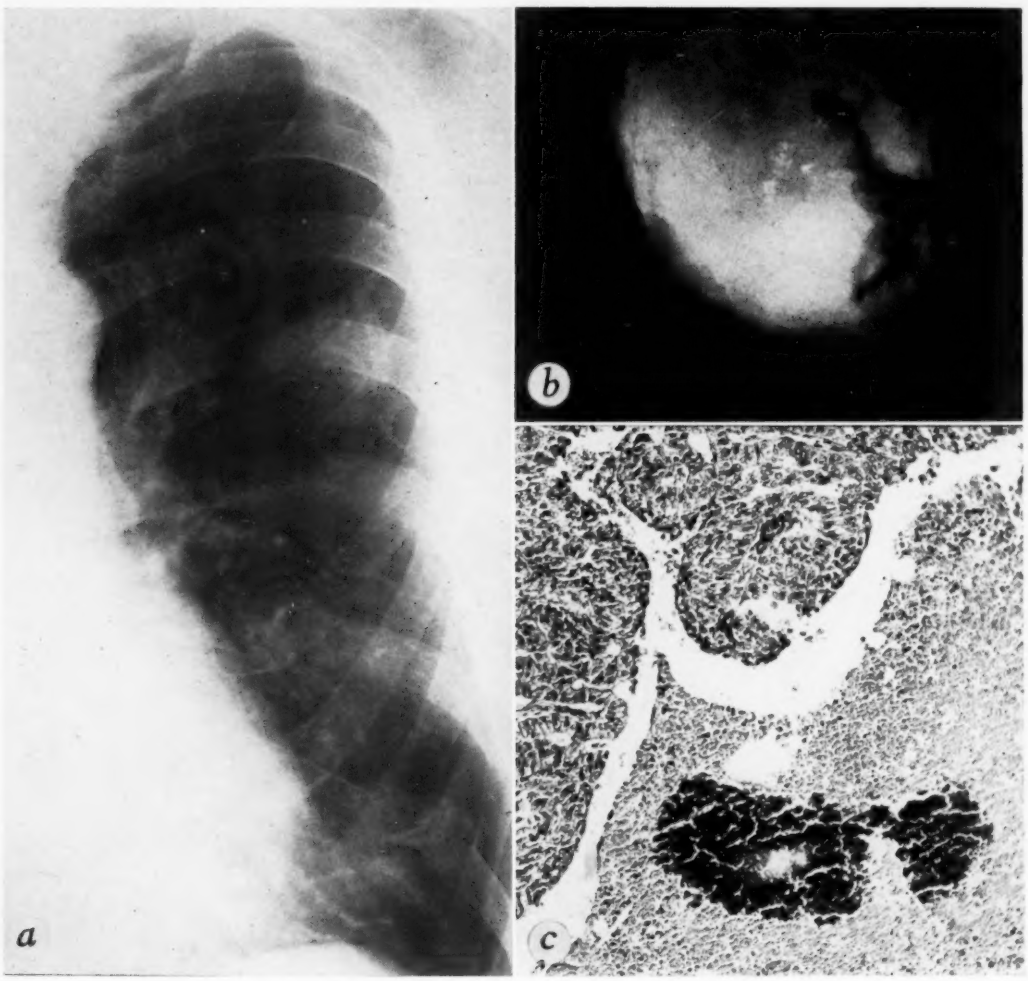


FIG. 6. Case IV. *a*. A 4 cm. nodular lesion may be seen in the left mid-lung field which did not appear to contain calcium. *b*. A roentgenogram of the excised lesion in *a* shows central areas of calcification. *c*. Section, taken through the calcified area in the lesion shown in *b*, reveals calcification in an area of necrotic large cell carcinoma, Grade 4 (von Kossa stain; ×95).

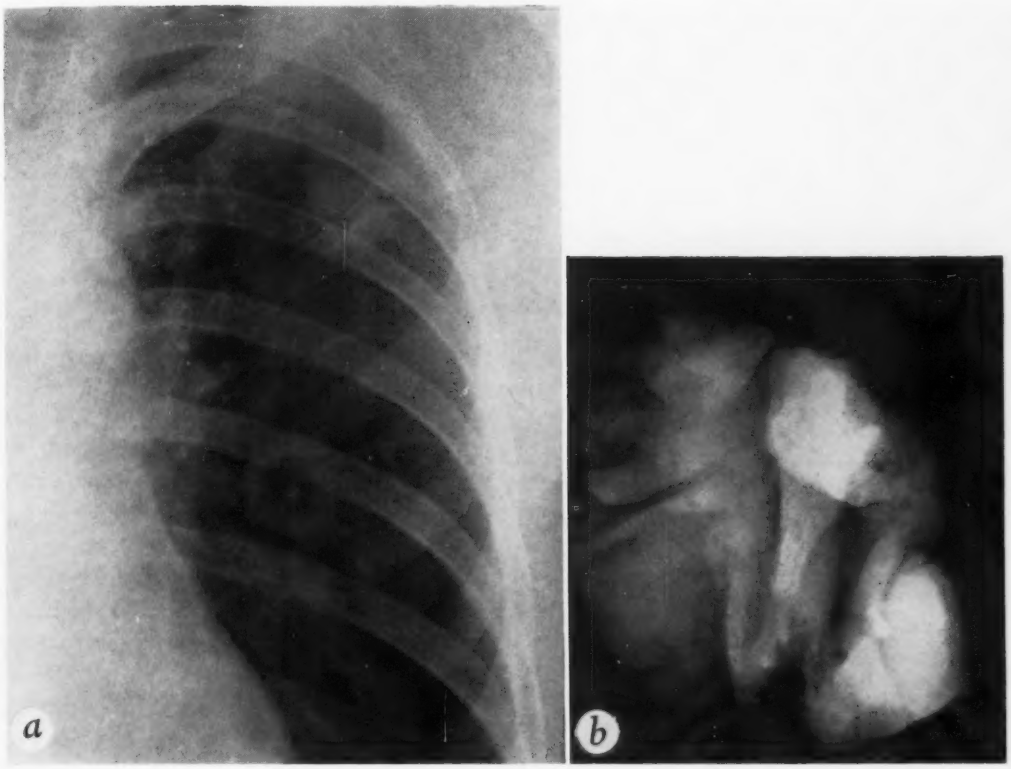


Fig. 7. Case v. *a*. A circumscribed lesion may be seen in the left upper lung field, which did not appear to contain calcification. *b*. A roentgenogram of the excised lesion shows some scattered calcification.

for years with no change in the past two to three years. Stereoscopic roentgenograms of the chest taken at this clinic on admission in March, 1951, disclosed an ovoid, somewhat lobulated mass 4 cm. in diameter, in the left lung just above the level of the hilus. There were multiple old fractures in the left ribs with some pleural thickening. The mass in the lung showed no evidence of calcification and the diagnosis of peripheral bronchogenic carcinoma was suggested. Roentgenograms made two weeks after admission demonstrated no change in the size of the lesion. Pertinent laboratory examinations, including tests of sputum for acid-fast bacilli and cytologic studies, and bronchoscopic examination, gave negative results. On exploratory thoracotomy, a lesion about the size of a golf ball was found in the midportion of the lateral surface of the left upper lobe. Biopsy of several hilar lymph nodes disclosed anthracosis. Because of the patient's age and lack of pulmonary reserve, a left upper lobectomy and lingulectomy were done. Study of the removed tissue revealed a large cell carcinoma, Grade 4, measuring 4 cm. in diameter. No involvement of the lymph nodes was found. Follow-up examination in October, 1951, showed no evidence of recurrence. Roentgenograms of the excised specimen (Fig. 6*b*) disclosed central calcification which on microscopic examination (Fig. 6*c*) was found in an area of necrotic tumor.

Case v. (Fig. 7 and 8). A forty-four year old white man was found, on chest survey, to have a circumscribed lesion in the left upper part of the lung six weeks prior to admission to the clinic in November, 1950. The patient was asymptomatic except for a chronic cigarette cough of many years' duration. Roentgenograms of the thorax taken two years prior to admission were reported as negative. Roentgenologic examination of the thorax on admission revealed a poorly circumscribed area of increased density in the posterior apical segment of the left upper lobe and a Ghon complex in the right lung (Fig. 7*a*). Both carcinoma and tuberculosis were considered. No contributory laboratory examinations were done. At operation a firm round mass was found in the left

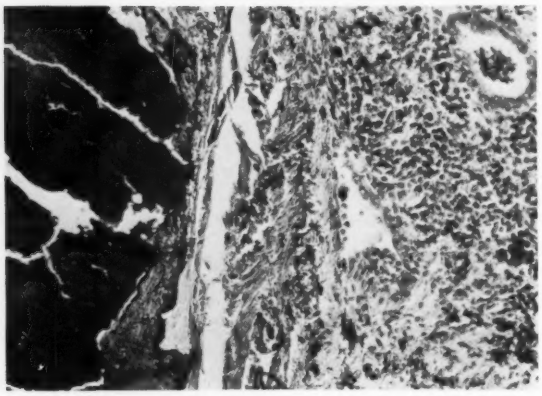


FIG. 8. Case v. Section, taken from a calcified area in the excised specimen (Fig. 7*b*.), reveals the calcium to be present in old healed scar tissue engulfed by an adenocarcinoma, Grade 4 (von Kossa stain; ×135).

upper lobe with some puckering of the overlying pleura. Biopsy revealed carcinoma, and left pneumonectomy and dissection of the left hilar lymph nodes were performed. The pathologist reported adenocarcinoma, Grade 4, measuring 2.5 by 2 by 2 cm. No bronchial involvement was found. Three regional lymph nodes contained the carcinoma. The patient made an uneventful recovery.

Follow-up examination at this clinic in March, 1952, revealed probable cerebral metastasis, and the patient succumbed in May, 1952. A roentgenogram of the specimen (Fig. 7*b*) revealed scattered calcification. Microscopic examination of the lesion showed that the calcification was present in old healed scar tissue (Fig. 8).

RESULTS

Of the total 207 specimens studied, 77 (37.2 per cent) showed roentgenologic evidence of calcification of the specimen and this finding was proved by microscopic examination of the specimen (Table I).

The highest percentage of calcification was found in the granulomas. Of the 90 specimens in this series 56 (62.2 per cent) showed roentgenologic evidence of calcification. Of these, 35 showed evidence of calcification on preoperative roentgenograms (Table II). Thirty-six (40 per cent) of the 90 granulomas showed calcification of the laminated variety (Fig. 1, inset). Four of these lesions also contained some punctate calcification, which on microscopic examination proved to be old

TABLE I

ROENTGENOGRAPHIC PATTERN OF CALCIFICATION IN SURGICALLY EXCISED LESIONS

Lesion	Total Cases	Calcification*					
		Laminated	Popcorn	Central	Punctate	Total	Per Cent
Benign							
Granuloma	90	36	0	9	11	56	62.2
Hamartoma	32	0	4	0	7	11	34.4
Miscellaneous	13	0	0	0	0	0	0
Total	135	36	4	9	18	67	49.6
Malignant							
Adenoma	14	0	0	1	1	2	14.3
Bronchogenic carcinoma	38	0	0	1	5	6	15.8
Metastatic lesion	20	0	0	1	1†	2	10.0
Total	72	0	0	3	7	10	13.9
Total	207	36	4	12	25	77	37.2

* Cases listed under predominant type only.
† Scattered in fine strands.

Table II

CALCIFICATION IN PREOPERATIVE ROENTGENOGRAMS AND IN ROENTGENOGRAMS OF SPECIMENS

Lesion	Total	Calcification in Roentgenograms	
		Before Operation	Specimen
Benign			
Granuloma	90	35	56
Hamartoma	32	11	11
Miscellaneous	13	0	0
Total	135	46	67
Malignant			
Adenoma	14	0	2
Carcinoma	38	1	6
Metastatic	20	0	2
Total	72	1	10

scarred and calcified inflammatory tissue. In the laminated variety, calcification was laid down between concentric rings of fibrous tissue thus supporting Good's theory of lamination as a mark of calcification. This characteristic pattern was not seen in any of the other pathologic types of specimens studied. Three of the 90 granulomas showed only central calcification. Six exhibited punctate calcification throughout the lesions. Three of the specimens with punctate calcification were positive for tuberculosis by bacteriologic culture and guinea pig inoculation, and one with central calcification only was positive for coccidioidomycosis by culture.

Of the 32 hamartomas studied, 11 (34.3 per cent) showed calcification. Four showed central calcification of the popcorn type, as seen in Figure 3*b*. The seven others showed only scattered calcification. In all 11, punctate calcification was shown on the preoperative roentgenograms. None of the seven hamartomas removed in the period from July 1, 1951, to December 31, 1952, showed calcification roentgenologically, whereas the percentage of calcified granulomas was in the same range in both the old and new series studied.

The series included 13 miscellaneous lesions: Five were bronchogenic cysts, one a chronic abscess, two unresolved pneumonitic processes, one a hemangioma, one a lymphangio-endothelioma, one a thymoma, and two mesotheliomas. None of these specimens showed calcification roentgenologically.

Seventy-two malignant lesions were studied, and 10 (13.9 per cent) showed roentgenologic evidence of calcification of the specimen and in one case the preoperative roentgenogram showed calcification in the region of the mass (Table 1 and II). This group included adenomas, primary bronchogenic carcinomas, and metastatic malignant lesions.

Fourteen adenomas were studied. Two of the gross specimens (14.3 per cent) showed calcification on the roentgenograms and on fluoroscopic examination. None of the preoperative roentgenograms showed evidence of calcification. Microscopic examination of the sectioned calcified area in one of these adenomas (Case III; Fig. 5*c*) proved it to be bronchial cartilage which has been surrounded by the slow growing tumor and had undergone ossification. Microscopic examination of the other specimen showed calcification in connective tissue distributed throughout the adenomatous tumor.

In six (15.8 per cent) of the 38 primary carcinomas, calcification was evident in roentgenograms of the specimen. One specimen showed central calcification which on microscopic examination (Case IV; Fig. 6*b* and *c*) revealed the calcium to be in necrotic tumor tissue. Microscopic examination of one of these specimens showed the calcium to be located in a Ghon lesion which had been engulfed by the growing mass. Calcification in the region of the mass was reported on the preoperative roentgenogram, and a pulmonary stone as well as carcinoma was suggested as the possible etiology.

Calcification in another lesion proved to

be located in calcified pleura which had been invaded by the tumor and could not be separated grossly from it. In the remaining specimens the calcium was contained in old healed scar tissue, presumably from a previously acquired chronic inflammatory process (Fig. 7 and 8). The preoperative roentgenograms in Case v as mentioned before showed, besides the mass in the left upper lobe, a Ghon complex in the right lung. A diagnosis of both carcinoma and tuberculosis was suggested by the roentgenologist.

Of the specimens of 20 metastatic lesions in this group, two (10 per cent) showed evidence of calcification on the roentgenogram of the specimen. In one of these, the calcification could not be seen fluoroscopically and a block cut through the area of greatest density proved to be the calcified area seen on the original specimen. Microscopically this showed calcium to be present in necrotic tumor cells. In the other specimen, the calcification had a fine strand-like appearance both fluoroscopically and roentgenographically. This also showed the calcium to be present in necrotic tumor cells, but to a greater degree than in the other metastatic lesion mentioned. The type of calcification found on roentgenographic examination of the specimens in the 77 cases is given in Table 1.

Laminagraphic Data. It was hoped that during the period from July, 1951, to December, 1952, laminagraphic studies could be carried out on a sufficient number of patients having surgical removal of their lesions to permit further evaluation. This procedure was followed in nine of the 58 cases studied; calcification was reported to be present in five of these, all of which were granulomas. The stereoscopic posteroanterior roentgenograms in these cases showed no evidence of calcification. The laminagrams in the other four cases did not show evidence of calcification.

SUMMARY AND CONCLUSIONS

Two hundred and seven cases in which the pathologic specimens were available were studied. Forty-nine and six tenths per cent of the benign and 13.9 per cent of the malignant lesions showed calcification by roentgenologic examination of the specimen.

This study indicates that calcification is present and can be demonstrated by roentgenologic means in a greater number of cases than we have been able to detect from the preoperative use of stereoscopic posteroanterior and lateral roentgenograms alone. The finding of calcium within these lesions does not, except for those showing the characteristic laminated and popcorn type of calcification, indicate that these lesions are benign.

The fact that the granulomas which had a laminated appearance roentgenologically did not contain viable organisms seems to be a significant finding. The mere presence of calcium in roentgenograms of the lesion in our experience, unless of the laminated type, does not mean that the lesion is inactive bacteriologically.

The number of laminagraphic examinations in cases in which pathologic material was available was too small to evaluate fully this procedure as a diagnostic aid, but evidence indicates that it may often show calcification to be present that is not evident on the stereoscopic posteroanterior and lateral roentgenograms of the thorax.

It can be concluded, therefore, from this study that a solitary circumscribed nodular lesion can be safely called "benign," from a roentgenologic standpoint, only if the laminated or popcorn type of calcification is clearly demonstrated.

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CALCIFIED INTRATHORACIC LESIONS CAUSED BY HISTOPLASMOSIS AND TUBERCULOSIS

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THE presence of intrathoracic calcifications in chest roentgenograms has been commonly interpreted as evidence of arrested or healing primary tuberculous infection. For a number of years the accuracy of this interpretation has been questioned. This has been particularly true in the endemic area of histoplasmosis where it has been shown that in most cases this particular disease is responsible for the calcifications. It is our intention to present further evidence that histoplasmosis is the usual cause of pulmonary calcifications in this region and to indicate certain characteristics of the calcifications which may be helpful in differentiating those caused by histoplasmosis from those of tuberculous etiology.

REVIEW OF THE LITERATURE

Opie and his associates[7,11] in 1926 and in 1929 observed appreciable numbers of children with pulmonary or mediastinal calcific lesions who reacted negatively to tuberculin. In 1937 Nelson, *et al.*[10] found that 13 of 27 children from Cincinnati with intrathoracic calcifications had a negative skin reaction to purified protein derivative (PPD) or old tuberculin (OT).

Gass and his co-workers[5] in 1938 carried out tuberculin sensitivity tests in 1,015 children from central Tennessee. Intrathoracic calcifications were seen in approximately the same number of positive reactors to tuberculin (51.1 per cent) as in the group of negative reactors (48.1 per cent). They concluded that a considerable proportion of children with "evidence of tuberculous infection" do not have a positive tuberculin test.

Long and Stearns[9] reviewed 53,070 chest photofluorograms and showed that intrathoracic calcifications in individuals living in an area bounded roughly by Oglethorpe, Georgia; Jefferson Barracks, Missouri; Little Rock, Arkansas; and Columbus, Ohio were more frequent and were larger and more numerous than in the chests of persons from other parts of the country.

Gass and associates[6] were able to observe the development of calcified lesions in a number of children whose tuberculin skin tests remained negative. This study suggested either that tuberculin skin tests were not reliable or that there were agents other than tuberculosis causing the calcifications.

In this regard, Cox and Smith[4] and Aronson, Saylor and Parr[1] have shown that Coccidioides immitis produces a primary complex which undergoes calcification and which is indistinguishable from that of tuberculosis.

Most pertinent to our study were the observations by Christie and Peterson[2] who demonstrated that of 78 Tennessee children with intrathoracic calcifications, only 32 per cent reacted to tuberculin, but 87 per cent reacted to histoplasmin. From this study and his own material, Palmer[12] concluded that a mild (probably subclinical) form of histoplasmosis (or infection with an immunologically related organism) is responsible for a high proportion of calcifications seen in the roentgenograms of tuberculin negative reactors.

Zwerling and Palmer,[19] in 1945 made an attempt to differentiate between the calcifications presumed to be the result of tuberculosis (positive PPD, negative histoplasmin) and those presumed to be due to histoplasmosis (negative PPD, positive

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histoplasmin). Of 57 of their cases in which the calcification measured 2 cm. or more in diameter, 44 (75 per cent) were histoplasmin positive and tuberculin negative. Only 3 reacted to tuberculin alone. However, none of these cases was proved by demonstration of the organism. They concluded that there were no striking characteristic features of the individual lesions which would be of value in the differentiation, except scattered, multiple bilateral calcifications which were considered to be of histoplasmic origin.

High, *et al.*[8] skin tested 108 persons in whom 5 or more distinct calcareous deposits were present in each lung. No case was found which reacted to tuberculin alone. Eighty-six per cent reacted to histoplasmin alone and 10 per cent reacted to both tuberculin and histoplasmin. They concluded that such multiple pulmonary calcifications were not frequently caused by tubercle bacilli, but probably by the agent producing sensitivity to histoplasmin.

Silverman[16] in 1950 reviewed the historic and epidemiologic features of histoplasmosis and stated that perhaps the only roentgen finding which alone might be reliably interpreted as the result of Histoplasma infection was disseminated intrathoracic calcification.

Straub and Schwarz[17] in 1955 studied 105 consecutive autopsies of patients dying from diseases not primarily involving the lungs. A healed intrathoracic calcified primary complex containing a stainable fungus morphologically consistent with Histoplasma capsulatum was found in 67 per cent of the cases. If Histoplasma capsulatum were not demonstrated and the microscopic picture showed the general characteristics of healed tuberculous foci, they were considered to be of tuberculous origin. The primary pulmonary lesions were divided into small and large foci, the small being 4 mm. or less in diameter and the large 5 mm. or more. Similarly, the calcified lymph nodes were classified according to size as small (less than 1 cm. in diameter) and large (1 cm. or more). From their observations they concluded that a primary focus measuring 5 mm. or more or a calcified lymph node 1 cm. in diameter or over was caused by Histoplasma capsulatum in 4 out of 5 instances.

MATERIAL AND METHODS

The present report is based upon a study of a number of individuals in whom intrathoracic calcifications were demonstrable in chest roentgenograms. Our material is divided into four groups.

Group 1: In this group are included 51 persons from Cincinnati (an endemic area of histoplasmosis) in whom pulmonary and/or mediastinal calcifications were apparent on 70 mm. photofluorograms. Routine posteroanterior and lateral 14×17 inch teleroentgenograms of the chest and skin tests with tuberculin and histoplasmin were obtained on each individual.

Group 2: Unselected 14×17 chest roentgenograms of 255 individuals living in New York City (a nonendemic area of histoplasmosis) are included in this group. Fifty-nine revealed intrathoracic calcific lesions. No skin tests were available in this group.*

Group 3: This group comprises 355 posteroanterior teleroentgenograms of the chest in individuals living in Cincinnati, mostly employees of the Cincinnati General Hospital. Calcifications were found in 101 of these individuals. No skin tests were obtained.

Group 4: This group consists of 24 individuals with proved histoplasmosis in whom calcifications were visible on chest roentgenograms. Histoplasma capsulatum was demonstrated at autopsy in 23 and at surgery in one. Among the autopsied cases, a healed primary intrathoracic complex was demonstrated in 19 patients and Histoplasma capsulatum was identified in the calcified pulmonary focus, mediastinal lymph nodes, or both. In the remaining 4 cases the organism was found in calcific hepatic lesions in two, in a large abdominal

* The films from New York were obtained through the courtesy of Dr. Hans Abeles, Assistant Director, Bureau of Tuberculosis, City of New York Department of Health.

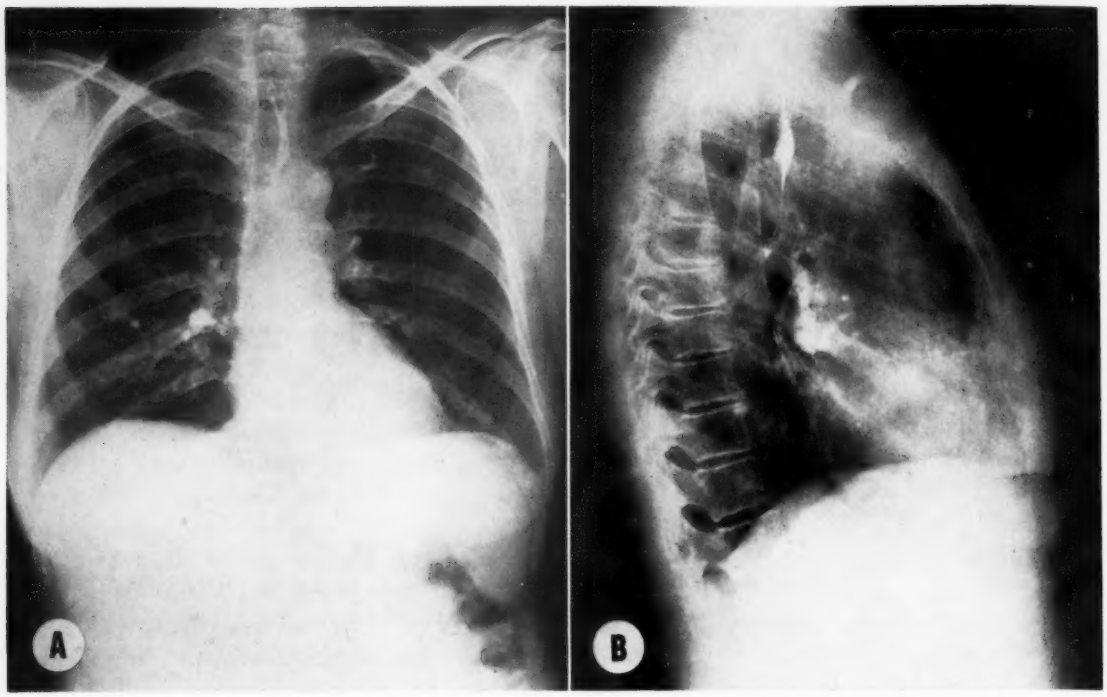

FIG. 1. Female, aged seventy. A-2576. (*A*) Posteroanterior chest roentgenogram. Large primary focus in the right middle lobe and a large hilar calcified (stippled) lymph node. H. capsulatum was demonstrated in the components of the primary complex, microscopically. (*B*) Same case. Lateral view.

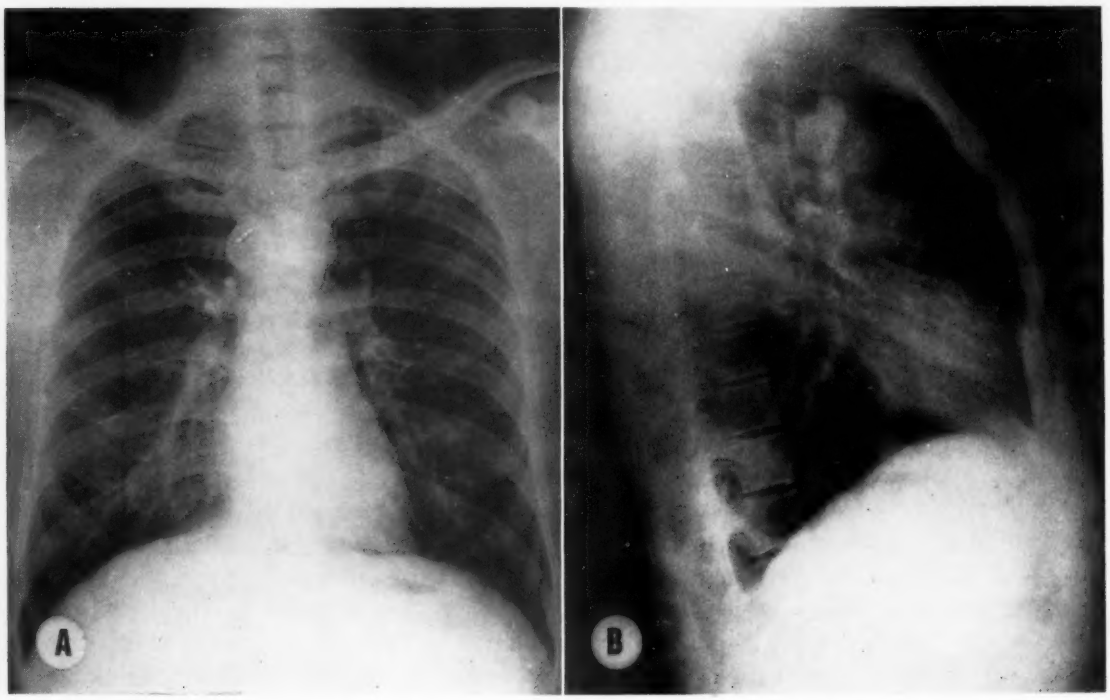

FIG. 2. Male, aged thirty-nine. (*A*) There are large lymph nodes in the right hilar and paratracheal areas with numerous stippled calcifications. Histoplasmin skin test positive, tuberculin negative. (*B*) Same case. Lateral view.

Table I

SIZE OF CALCIFICATIONS

Skin Tests	Group I	
	5 mm. or less	6 mm. or more
positive histoplasmin, negative tuberculin	1	30
positive tuberculin, negative histoplasmin	2*	0
positive histoplasmin and tuberculin	0	8
negative histoplasmin and tuberculin	0	10†
Total	3	48

* Both foreign born visitors in the United States.

† Skin reactivity decreases in persons over forty-five years of age; this may be responsible in part for the large number of nonreactors.[16]

lymph node once, and in still another instance, in the adrenals. These 4 cases are included because the abdominal involvement must have been secondary to the intrathoracic calcified lesions which were also present. Unfortunately, microscopic study of the intrathoracic calcifications in the 4 cases was not obtained.

The identification of calcifications was based on the following criteria:

1. Irregular shadows having the densities of calcium. In this category were included the "stippled" calcifications commonly arranged in groups from three to ten or more each measuring from 1 to 5 mm. in diameter, which undoubtedly mostly represented calcified lymph nodes.

2. Rounded homogeneous shadows, if they were very dense and were located apart from the hilar areas and if no blood vessels of similar caliber could be traced to them.

3. Laminated shadows.

RESULTS

In Group 1 (Table 1) only 3 cases showed calcific lesions measuring 5 mm. or less in diameter (6 per cent). Two of the 3 were positive to tuberculin and negative to histoplasmin and the other was positive to histoplasmin and negative to tuberculin. In the remaining 48 individuals, the roentgenograms showed calcific lesions measuring 6 mm. or more in diameter. Of these, 30 (59 per cent) reacted positively to histoplasmin alone. None reacted to tuberculin alone. Eight were positive to both antigens and 10 did not react to either. Forty-six of the 51 revealed a definite calcified primary complex (pulmonary focus plus regional lymph nodes).

In Group 2 (Table II) 33 of the cases (56 per cent) revealed calcifications 5 mm. or less in diameter while in 26 (44 per cent) the calcifications measured 6 mm. or more. None of the chest roentgenograms in this

Table II

Group	5 mm. or less		6 mm. or more		"stippled"		Total No. of Cases
1. From Cincinnati Skin tested with PPD and tuberculin	3	6%	48	94%	38	75%	51
2. From New York No skin tests	33	56%	26	44%	16	27%	59
3. From Cincinnati No skin tests	21	21%	80	79%	70	69%	101
4. From Cincinnati Proved microscopically	2	8%	22	92%	16	67%	24
							235

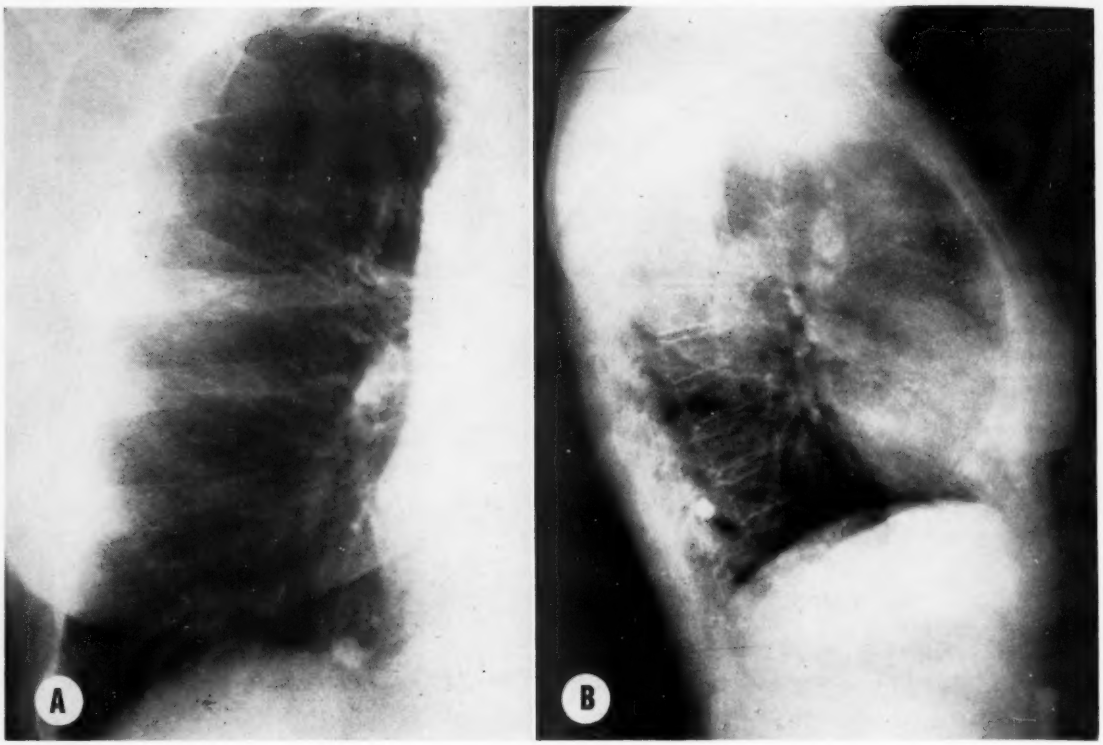

FIG. 3. Female, aged sixty-five. (*A*) There is a large primary focus in the right lower lobe and stippled calcified lymph nodes in the right hilus and paratracheal area. Histoplasmin skin test positive, tuberculin negative. This patient also had multiple splenic calcifications. (*B*) Same case. Lateral view.

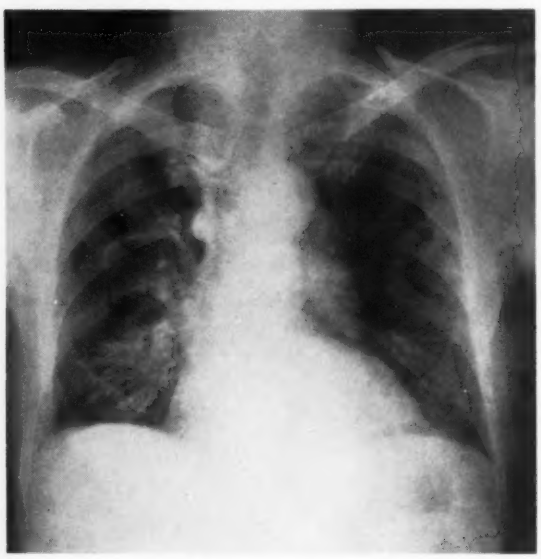

FIG. 4. Male, aged seventy-five. A-2804. There are two calcific lesions in the apex of the right upper lobe which could either be primary foci or calcifications in a healed post-primary right upper lobe histoplasmosis. There is a large calcified (stippled) paratracheal lymph node. H. capsulatum was demonstrated on microscopic section.

FIG. 5. Female, aged seventy-one. A-3220. There is a large laminated calcified primary focus in the left upper lobe. She also had multiple splenic calcifications. H. capsulatum was demonstrated in the pulmonary focus and splenic lesions.

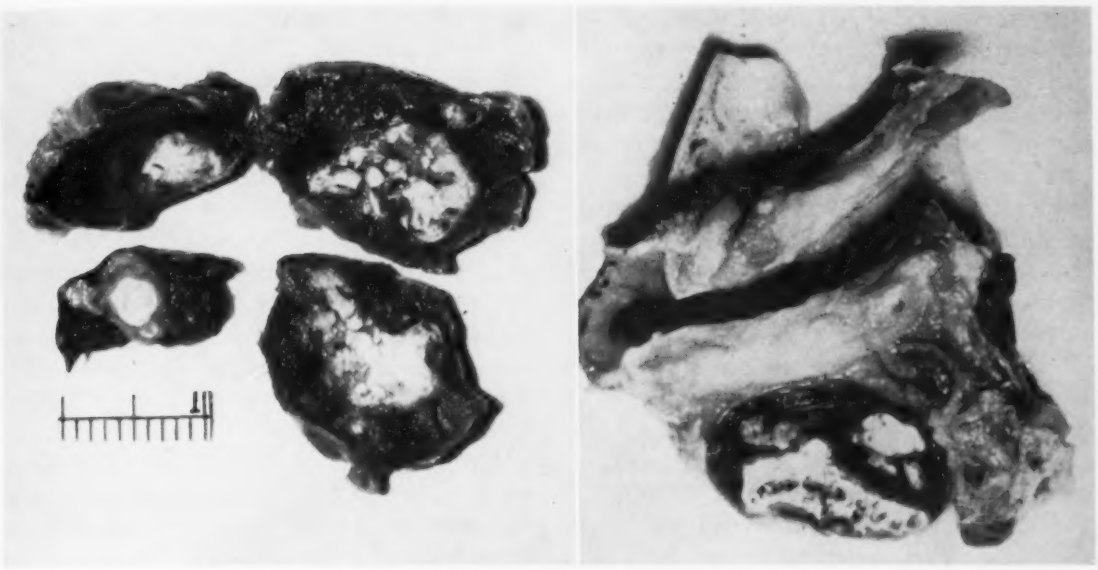

Fig. 6. The anatomic substrate of the "stippling" are discrete calcific foci within the area of old caseation necrosis in lung tissue or lymph nodes.

group showed calcified paratracheal lymph nodes, but some demonstrated calcified hilar lymph nodes.

Of the 101 cases with calcifications in Group 3, in 80 persons (80 per cent) the calcifications measured 6 mm. or more, while in 21 (20 per cent) they measured 5 mm. or less (Table II). In 6 of the 80 calcified paratracheal lymph nodes were seen.

In Group 4 only 2 persons (8 per cent) had calcifications in the chest measuring 5 mm. or less while 22 (92 per cent) revealed calcified lesions 6 mm. or more in diameter (Table II). Two of the cases showed calcified paratracheal lymph nodes and 5 were found to have, in addition, multiple splenic calcifications.

In a very large percentage of cases, "stippled" calcifications which are clearly recognizable as being within lymph nodes were noted. A special study of these lesions was made. The results are listed in Table II. It is apparent that "stippled" calcification within lymph nodes was present in over two thirds of the Cincinnati cases and in less than one third of the cases from New York. We, therefore, believe that the presence of this type of intrathoracic lesion is another diagnostic point in favor of the histoplasmic origin of a given calcification.

DISCUSSION

The etiology of intrathoracic calcifications in individuals with negative PPD was clarified with the discovery of skin sensitivity to coccidiodin and especially to histoplasmin and the demonstration of primary intrathoracic complexes caused by Coccidioides immitis[1,4] and Histoplasma capsulatum in autopsy material.[13,14] The distinction between calcified intrathoracic lesions caused by H. capsulatum and M. tuberculosis has, therefore, become very important. The first attempt at differentiation among calcified lesions caused by these organisms was made by Zwerling and Palmer[19] in 1945. Although a significant incidence of positive skin reactions to histoplasmin among individuals with large intrathoracic calcifications had been repeatedly observed, more conclusive evidence of the relationship between such calcifications was lacking until the recent work of Straub and Schwarz.[17] In the present study we have demonstrated the presence of significantly greater percentages of large calcified intrathoracic lesions (measuring 6 mm. or more) in the groups from the endemic area of Cincinnati (Groups 1, 3 and 4) than in the group from the nonendemic area of New York (Group 2). We

therefore conclude, on the basis of our own observations and those of Straub and Schwarz[17] that the larger calcified intrathoracic lesions seen in roentgenograms of the individuals living in the endemic area of histoplasmosis are caused in most instances by H. capsulatum. The presence of multiple splenic calcifications in some of the cases of proved histoplasmosis lends further support in favor of the histoplasmic origin of the chest calcifications. In a study of calcified splenic foci, the present authors found that those which were either multiple (more than 5) or were "laminated" (regardless of the number), in most instances, were caused by histoplasmosis.[14,15]

The relatively large percentage of individuals with calcifications measuring 6 mm. or more in the group from New York may be explained on the basis of migration from the endemic areas. This was found to be the case in a study by Straub and Schwarz[18] in Tucson, Arizona which is an area known to be endemic for coccidioidomycosis. Forty consecutive autopsies were studied in this city and in 19 cases (almost 50 per cent) a histoplasmic primary complex was found. In only 8 cases was Coccidioides immitis demonstrated in the intrathoracic lesions. Thirteen of the 19 cases having a primary histoplasmic complex had arrived from the endemic area of histoplasmosis.

A similar experience (with skin testing only) was recently reported by Comstock, *et al.*[3] among a group of patients with calcified and noncalcified pulmonary nodules ("coin" lesions). Sixty-six per cent had a positive histoplasmin skin reaction even though this study was undertaken in a nonendemic area of histoplasmosis (Columbus, Georgia).

SUMMARY AND CONCLUSIONS

A short review of the literature concerning the calcific intrathoracic lesions in negative reactors to tuberculin has been given. At present there is no doubt of a cause and effect relationship between Histoplasma capsulatum and pulmonary calcifications in the endemic area. We believe that, in most instances, calcified histoplasmic intrathoracic lesions can be differentiated from those caused by tuberculosis on the basis of size and the presence of "stippling." Calcifications measuring 6 mm. or more and "stippled" calcifications in individuals living in the endemic area of histoplasmosis are caused, in most instances, by histoplasmosis. The presence of multiple or laminated splenic calcifications in patients with intrathoracic calcifications can be decisive in considering histoplasmosis as the cause of intrathoracic calcifications.

Groups from Cincinnati and New York were chosen in order to make a comparison between an area of high incidence of positive histoplasmin and low incidence of tuberculin skin tests (Cincinnati) with an area in which the reverse is found (New York).

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This study was greatly facilitated by the material and help obtained from Drs. B. Felson, L. Rosenberg, Hans Abeles and Gerald L. Baum.

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SEGMENTAL LOCALIZATION OF UPPER LOBE TUBERCULOSIS*

THE RARITY OF ANTERIOR INVOLVEMENT

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THE predominantly posterior involvement of the upper lungs by early adult-type pulmonary tuberculosis, although well-known to pathologists, is only casually mentioned in the roentgen-clinical literature.[9,11] This article will describe the incidence of posterior segment upper lobe involvement, offer a theory for its occurrence, and give one example of unusual localization of tuberculosis in the anterior segment of the upper lobe. The importance of the predominant predilection for posterior segment involvement will be emphasized.

In 1923, Wessler and Jaches[12] first described the infraclavicular origin of adult-type pulmonary tuberculosis. Independently, studies by Assmann[1] stressed the importance of this "infraclavicular infiltrate" and correctly localized it to the apical and posterior portions of the upper lobes. Although most pathologists realize that incipient adult tuberculosis begins almost always in the apical and posterior areas of the upper lobes and the superior portions of the lower lobes, few, if any, clinicians or radiologists have focused attention on posterior localization in the roentgen differential diagnosis of tuberculosis.

Rich[10] in 1933 collected the numerous theories advanced to explain the usual location of the early tuberculous infiltrate, and Dock[4] in 1946, on the basis of clinical observation of physiologic data supplied an ingenious theory for apical and subapical localization of early adult pulmonary tuberculosis.

As soon as lobectomy became a practical reality, thoracic surgeons began to perform segmental resection for limited disease processes. These operations provided the impetus for the careful study of the anatomic subdivisions of the lung lobes done by Brock,[3] Glass[5] and Jackson and Huber.[6] These studies culminated in the important work of Boyden[2] which, to date, remains the classic authoritative study of the segmental anatomy of the lung.

Incidence of Segmental Localization of Early Upper Lobe Tuberculosis. One hundred cases of adult-type pulmonary tuberculosis were selected at random from the Pulmonary Service of Montefiore Hospital. All these patients had sputums positive for tubercle bacilli. Examination of the chest roentgenograms done in the posteroanterior and lateral projections was undertaken and data as to bronchopulmonary segment localization were tabulated. Cases were included only if the disease was unilateral and if two segments or less of the upper lobes were involved.

The terminology used in the tabulation was that accepted by the International College of Oto-rhino-laryngology in London in 1949, and is basically the classification of Jackson and Huber (Fig. 1). In this classification, the right upper lobe is divided into apical, posterior and anterior segments. The left upper lobe is divided into apical-posterior, anterior and superior and inferior lingular segments.

It may be seen in Table 1 that of the 100

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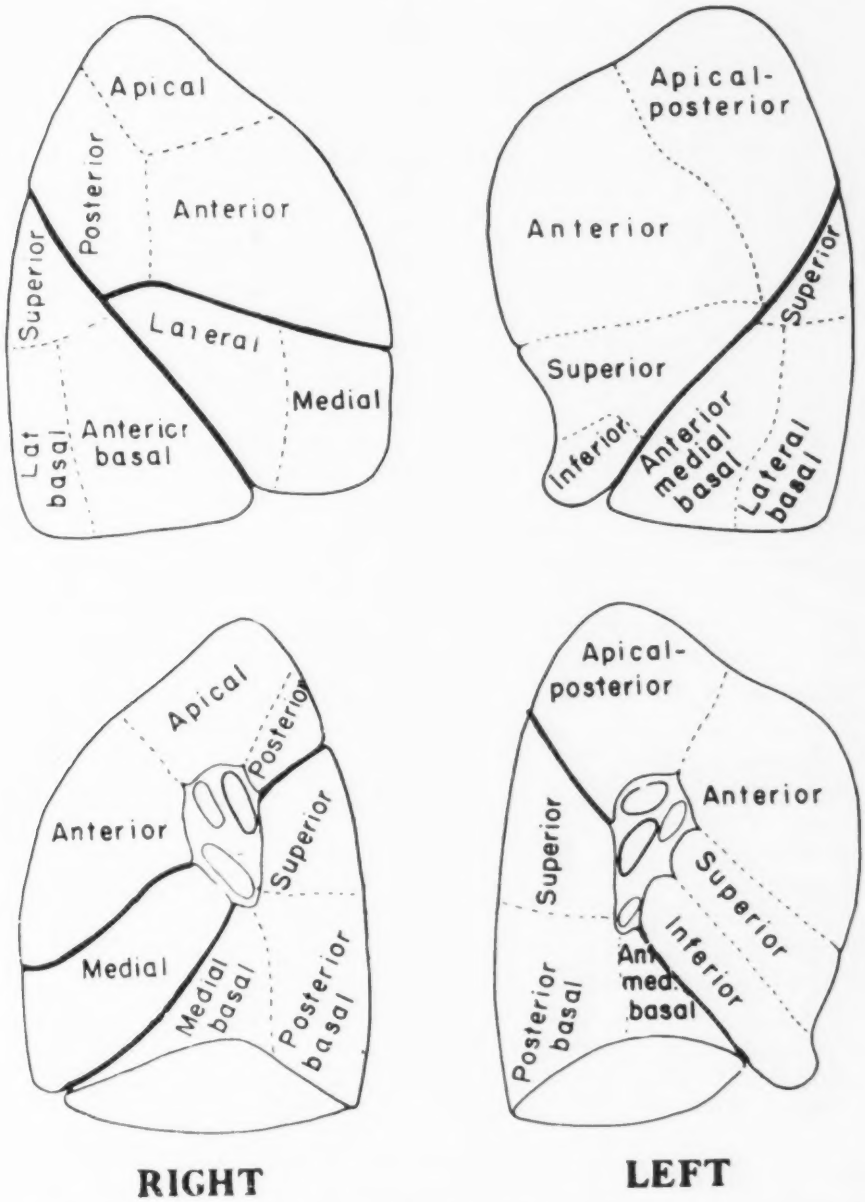

Fig. 1. The Jackson and Huber classification of the bronchopulmonary segments.

cases studied, 70 showed combined involvement of the apical and posterior segments of the upper lobes. In 20 there was pure posterior segmental localization and 10 demonstrated pure apical disease. Thus, in 90 per cent of the cases, posterior segmental involvement by minimal tuberculosis was found. No case of pure anterior segmental involvement in this series was encountered. Such data clearly indicate that an infiltrate or mass confined to the anterior segment of an upper lobe in an adult has only a remote change of being tuberculous.

Theory for the Posterior Preponderance of Pulmonary Tuberculosis in the Upper Lobes. Dock's classic theory for apical and subapical localization of adult-type pulmonary tuberculosis will be briefly reviewed here. A summary of Dock's observations follows:

1. Pulmonary tuberculosis is uncommon

TABLE I

SEGMENTAL LOCALIZATION OF MINIMAL TUBERCULOSIS

Total Number of Cases Studied		100
Right Upper Lobe		
isolated apical	10	
isolated posterior	20	
apical and posterior	31	
Total	61	
Left Upper Lobe		
apical-posterior	39	

in people with rheumatic heart disease in which pulmonary hypertension exists.

2. Pulmonary tuberculosis is extremely common in pulmonary stenosis (as high as 90 per cent in some series) where pulmonary arterial pressure is low.

3. In the erect posture the weight of the column of blood which supplies the apical portions of the upper lobes almost equals the main pulmonary arterial pressure as determined by cardiac catheterization. Thus pulmonary blood flow cannot be maintained.

4. The asthenic, slender individuals with long chests have a higher incidence of pulmonary tuberculosis than the general population. In these individuals, the distance from the main pulmonary artery to the apex is increased, so that in the erect posture, blood flow is even poorer than in the average or hypersthenic person.

5. Tuberculosis is more common in the right upper lobe than in the left. Blood originating from the right ventricle (Fig. 2) courses toward the left apex via a large, short pulmonary artery which breaks into lobar branches in the left lung. Conversely, the right pulmonary artery is long and narrow, arises from the main branch at an angle and descends toward the left, with consequent lowered pressure on this side.

Dock thus felt that "the pulmonary arteries can bring few antibodies to the apices as long as the patient was sitting or standing. Since even in inflamed tissue with vascular permeability, tissue fluid formation is dependent on an adequate intravascular pressure and since pulmonary arterial pressure in the apices is practically zero, removal of bacterial products by lymph or dilution by diffusion into the blood would be practically nil." Thus the susceptibility of the superior lung segments to tuberculosis is explained by Dock.

A further independent confirmation for Dock's postural theory comes from Medlar's[8] work with rabbits. These animals were intravenously inoculated with bovine type tuberculosis and held in the erect position with a harness for eight to ten hours a day. These rabbits normally develop tuberculosis in the dorsal and caudal areas. When sacrificed, although 4 of the 6 rabbits showed some disease in these caudal and dorsal regions, every animal demonstrated tuberculosis in the cephalic portion of the lungs.

Dock's theory is quite satisfactory in explaining the clinical, experimental and physiologic data known today. Although the reason for the juxta-apical localization of tuberculosis is clarified, the universal preponderance of tuberculosis for the posterior as opposed to the anterior segment of the upper lobes has not even been considered.

A knowledge of the more recent anatomic

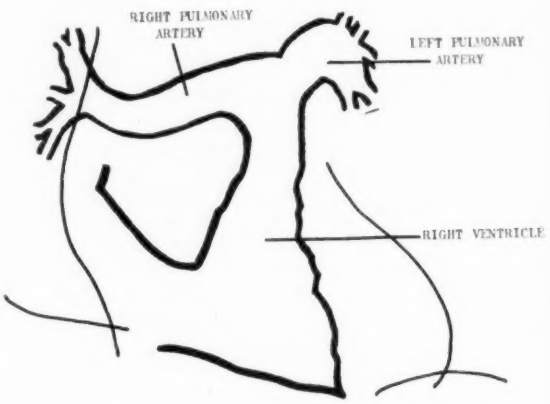

FIG. 2. Tracing of a normal angiocardiogram showing opacification of the right side of the heart. The left pulmonary artery is wide and short. The right pulmonary artery is longer and narrower and pursues a slightly downward course to the right. This difference accounts for the lower pulmonary arterial pressure on this side.

studies of the bronchopulmonary segments suggests the answer. Boyden's dissections of 50 lungs produced the generic pattern illustrated in Figure 3. When compared with Figure 1 (taken from Jackson and Huber), there is a marked inconsistency of relative location of the anterior and posterior segments of the upper lobes and the superior segment of the lower lobes. In the Jackson and Huber diagram, the anterior segment of each upper lobe lies only slightly lower than the posterior segment and extends above the superior segment of the lower lobes. In the critical anatomic dissections of Boyden, the apical, posterior and apical-posterior segments of the upper lobes and superior segments of the lower lobes lie on a definitely higher level, well above the anterior segments of each upper lobe.

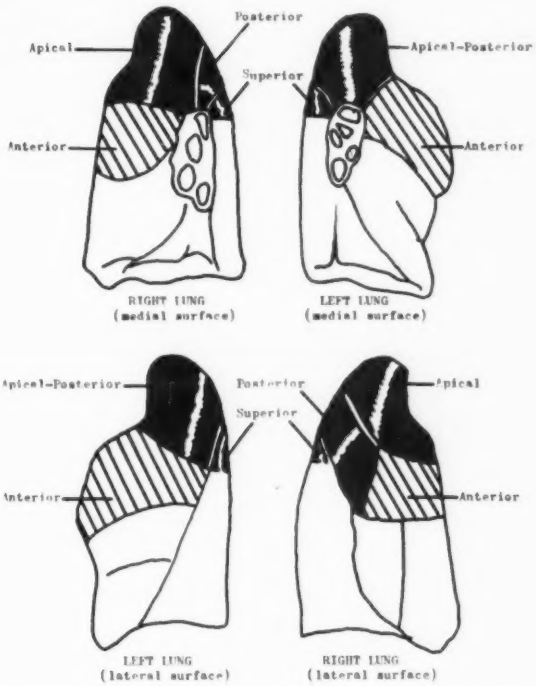

Fig. 3. Schematic modification of tracings of Boyden's diagrams of the average location of the bronchopulmonary segments in 50 carefully dissected postmortem specimens. Compare with Figure 1 and note that the apical and posterior divisions of the upper lobes and the upper margins of the superior segments of the lower lobes sit on a level above the anterior segments of the upper lobes.

These observations dovetail with Dock's theory. The apical and posterior segments of the right upper lobe, the apical-posterior segment of the left upper lobe and the superior segment of each lower lobe are the clearly defined *upper lung*. The *upper lung* segments serve as a unique physiologic unit characterized by poor blood circulation and resultantly act as an Achilles heel for the development of pulmonary tuberculosis.

There are two additional features not considered by Dock which lend further support to the concept of the anatomic-physiologic unity of the *upper lung*. Macklin[7] in 1932 demonstrated by roentgenograms of the chest taken in inspiration and expiration that the posterior and cephalad segments of the lungs show limited respiratory motion as compared with the more dependent portions.

Brock[4] in 1954 offered the theory of bronchial embolism, which he felt was by itself sufficient to explain the selective localization of tuberculosis. The apical, posterior and superior segments of the lungs have in common a characteristic direction of the bronchi supplying them; in the lateral recumbent and supine positions, these bronchi assume a vertical direction and favor the drainage of infected emboli into their respective segments.

We feel, therefore, that our *upper lung* concept is buttressed by the additional factors of dimished respiratory motion and ease of embolization.

Involvement of the anterior segment of the upper lobes by contiguity following disease in the apical and posterior segments is not unusual. Such cases have been deliberately omitted from consideration in this paper. Isolated involvement of the anterior segment of an upper lobe by adult-type tuberculosis is quite rare. One such case is now described.

REPORT OF A CASE

CM was a thirty-five year old Puerto Rican factory worker in whom an asymptomatic lesion was discovered on a mobile chest photofluorogram. On admission on December 3,

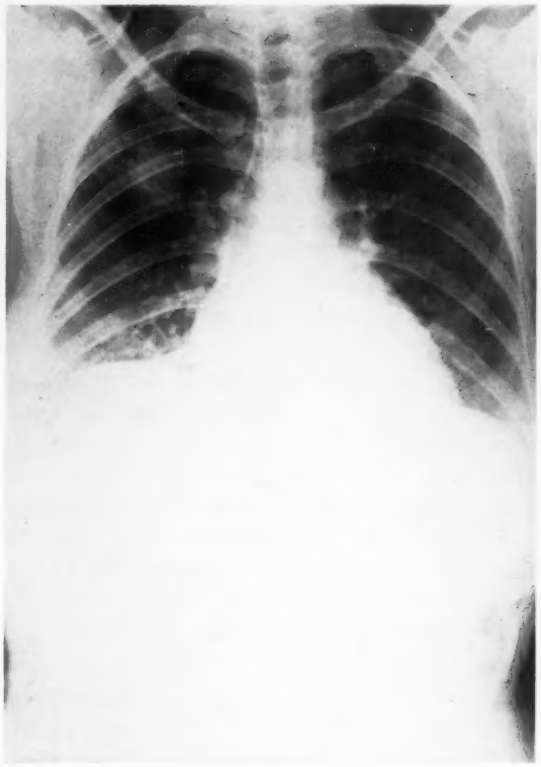

FIG. 4. Posteroanterior roentgenogram of the chest showing a large spheroid lesion in the right upper lobe.

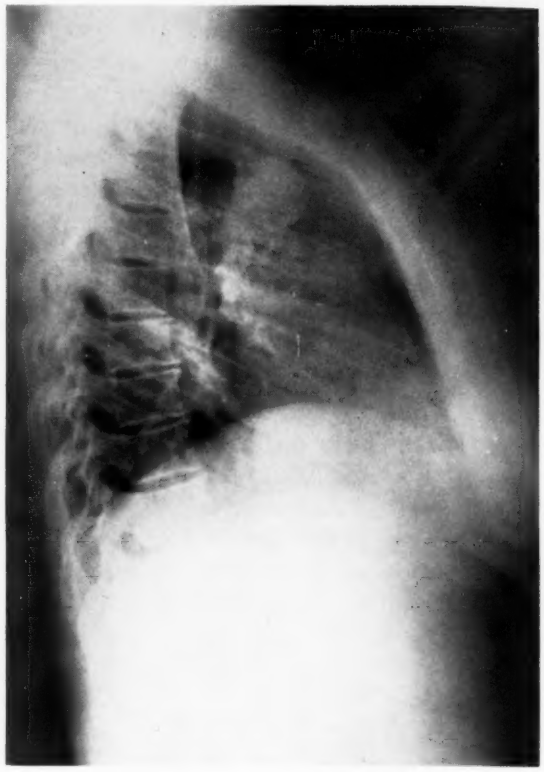

FIG. 5. Right lateral view of the chest indicating that the spheroid lesion noted on the posteroanterior roentgenogram lies in the anterior segment of the right upper lobe. This is a rare location for pulmonary tuberculosis, adult-type.

1955, she presented no abnormalities on physical examination except for an enlarged firm liver. The tuberculin test was strongly positive in a strength of 1–1000. A coccidiomycosis skin test was negative. On chest roentgenography, a spheroid lesion, 2.5 cm. in diameter was noted in the *anterior* segment of the right upper lobe (Fig. 4 and 5). In spite of the anterior localization of the lesion, a diagnosis of tuberculosis was entertained (a young Puerto Rican female with a positive tuberculin test).

After a preliminary period of INH and streptomycin therapy, an exploratory thoracotomy was performed on January 10, 1956. A spheroid mass, somewhat larger than noted on the roentgenograms, was seen in the anterior segment of the right upper lobe. A frozen section was interpreted as tuberculosis and a lobectomy was done. The patient made a good recovery in spite of a hydropneumothorax which developed on the eighth postoperative day. She was treated by repeated thoracentesis, antibiotics and specific antituberculous therapy.

Pathological Examination. The surgical specimen (a 3.5 cm., well demarcated, spheroid mass), showed tubercle bacilli on smear. Sections of the mass revealed a large central area of caseous necrosis and a marginal zone of inflammatory tissue. On the edge of the necrotic area there were fibroblasts lined up in radial fashion with a scattering of lymphocytes, plasma cells and phagocytes in dense collagenous connective tissue stroma. There were numerous lymphoid follicles and some of the small vessels showed thickening and fibrosis of their walls. A few Langhans type giant cells were found in the marginal inflammatory border. Nearby pulmonary alveoli showed areas of hemorrhage, accumulation of phagocytes and metaplastic alteration of septal cells. Diagnosis: Pulmonary tuberculosis.

SUMMARY AND CONCLUSIONS

1. Early adult-type pulmonary tuberculosis is almost always limited to the apical and posterior segments of the upper lobes. The roentgen demonstration of a lesion solely limited to the anterior segment of an upper lobe effectively excludes tuberculosis, as a general rule.

2. A case of pulmonary tuberculosis of the right upper lobe limited to the anterior segment is presented as a rare exception.

3. In a series of 100 consecutive cases, no other such lesion could be found.

4. The work of Dock, Brock, Macklin and Boyden is briefly reviewed and their divergent viewpoints are combined into our concept of the *upper lung*. The *upper lung* lies above all other segments of the lung, comprises the apical, and posterior segments of the upper lobes and the superior segments of the lower lobes and is a unique anatomico-pathologic unit characterized by poor blood circulation, diminished respiratory ventilation and a distribution of the bronchi favoring embolization.

5. These data, anatomic studies and concepts serve to explain the extreme rarity of early tuberculosis isolated to the anterior segment of an upper lobe.

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BRONCHIAL CARCINOMA ARISING IN A LUNG CYST*

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MALIGNANT transformation within a lung cyst is generally regarded as a highly remote possibility. Korol[3,4] has called attention to this possibility and he reported a series in which the incidence of ultimate malignant change has been quite high. Of 40 carefully followed cases of congenital pulmonary cysts 10 (25 per cent) have developed carcinoma of the lung.[4] Conversely, a control group comprised of 60 cases of diffuse bullous emphysema followed for the same prolonged period of time had shown not a single instance of bronchial carcinoma.

The above correlation has considerable surgical significance and has prompted Larkin and Phillips[5] to state that "the possibility of malignant degeneration in the wall of a cyst forms another indication for removal of these cysts whenever feasible." In the present paper, we would like to present a case in which serial roentgenograms depict the evolution of a bronchial carcinoma in the wall of a lung cyst. In this case, the relationship between the carcinoma and the cyst seems proven beyond doubt.

REPORT OF A CASE

The patient, F.P.W., was a fifty-four year old white salesman whom we first saw in October, 1953, because of a steadily enlarging nodule in the upper lobe of the right lung. Over the preceding eight years the patient had had a spontaneous pneumothorax on three separate occasions, each time on the right side. Chest roentgenograms obtained at the time of these episodes were reported as showing a cyst in the right upper lobe. In January, 1951, a routine chest roentgenogram revealed a small nodular density measuring less than 1 cm. in diameter lying in close apposition to the inferior margin of the cyst (Fig. 1). Over the next 16 months the nodule increased very little in size (Fig. 2), but when another follow-up film was obtained 13 months later the nodule had attained a diameter of 3.5 cm. (Fig. 3). Observation was continued until we saw him in October, 1953, 33 months after the nodule was detected, by which time it was 5.5 cm. in size (Fig. 4).

The patient stated that he felt fine. For the preceding ten years he had had a cough productive of several ounces of thick mucoid sputum daily, mostly in the morning. The character of the cough had not changed. There had been no hemoptysis, wheeze, chest pain, anorexia nor weight loss. He had smoked two packs of cigarettes daily for the past 30 years. Past history including a review of systems was not otherwise contributory.

The patient appeared healthy and the physical examination was negative. Breath sounds were clear and there were no rales or other

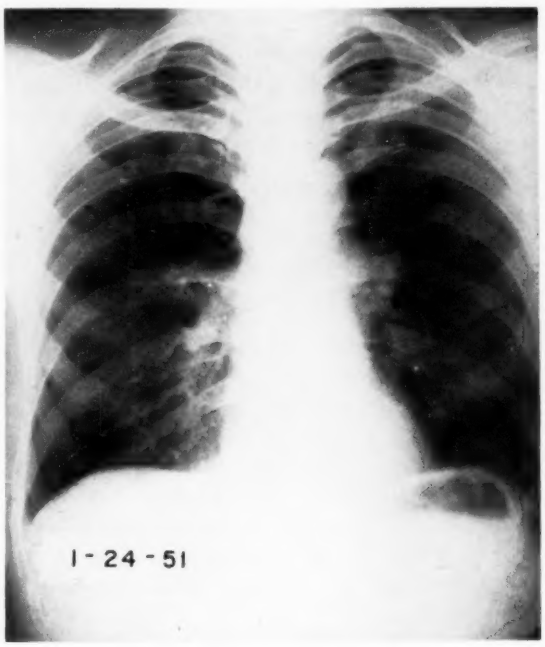

FIG. 1. First chest roentgenogram showing small nodular density beneath the inferior margin of right apical cyst.

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Fig. 2. Chest roentgenogram obtained 16 months later. There has been only a minimal increase in the size of the solitary pulmonary nodule.

adventitious sounds on normal breathing, inspiration, forced expiration or coughing.

On October 28, 1953, under endotracheal ether-oxygen anesthesia the right pleural space

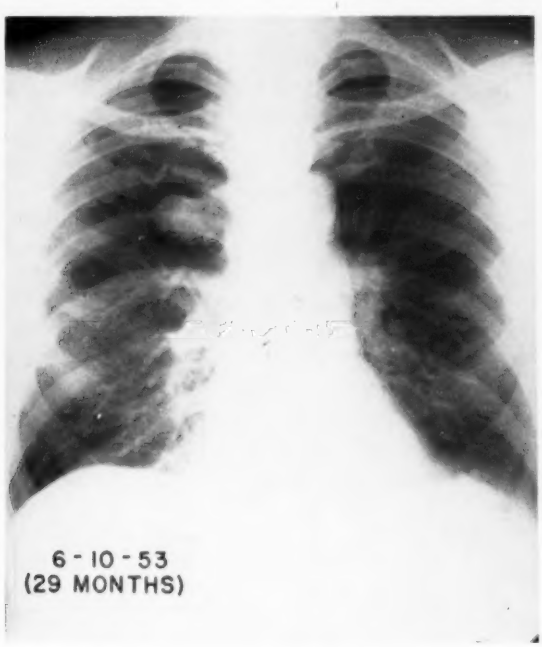

Fig. 3. Chest roentgenogram obtained twenty-nine months after the initial roentgenogram showing a considerable increase in the size of the nodule.

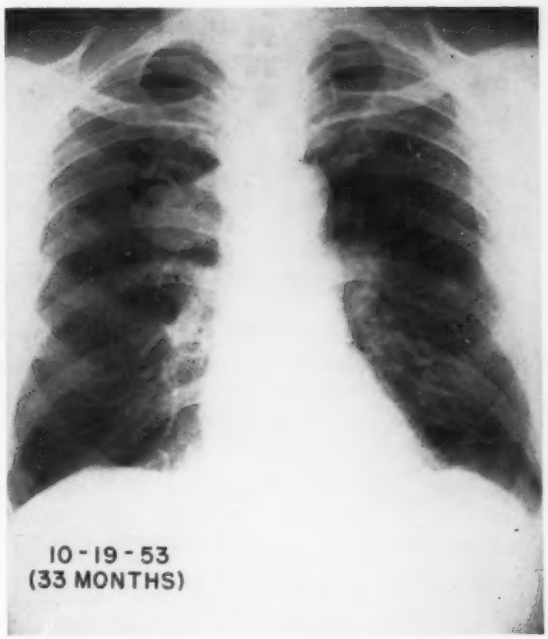

Fig. 4. Chest roentgenogram taken 33 months after the initial roentgenogram. Only after this examination was the patient seen in surgical consultation.

was entered through the bed of the subperiosteally excised fifth rib. The entire upper lobe was densely adherent to the chest wall. After freeing up these adhesions the apex of the upper lobe was found to be cystic in character and a large firm tumor could be palpated in the paramediastinal region where it had invaded the lateral wall of the trachea and the superior vena cava. An azygos lymph node was markedly enlarged. A pneumonectomy was performed, the involved portions of the trachea and superior vena cava were excised and their continuity restored. All contiguous mediastinal lymph nodes, some of which were greatly enlarged, were removed *en bloc* with the lung. Recovery was uneventful.

Pathologic examination showed a 6 cm. tumor mass lying within the right upper lobe but extending into the hilus and through the mediastinal pleura. The tumor bulged upward into a trabeculated unilocular pulmonary cyst. Microscopic study showed the neoplasm to consist of undifferentiated carcinoma. In only one of the mediastinal lymph nodes could metastatic carcinoma be demonstrated. The wall of the cyst consisted of dense connective tissue without any lining epithelium. Fibrous trabeculae were prominent. On the basis of these findings

it was impossible to determine whether the cyst was of congenital or acquired etiology, although the presence of dystrophic calcification in some areas certainly attested to its long duration.

A follow-up inquiry obtained two years and three months postoperatively revealed the patient still to be in good health and free of any evidence of recurrence.

DISCUSSION

The great difference between the rates of malignant transformation in the congenital as opposed to the acquired cysts in Korol's cases[3,4] may, perhaps, be attributed to the fact that his distinction was based wholly upon clinical and roentgenologic observations. On the other hand, one cannot deny the fact that bronchial carcinoma may occur as a complication of pulmonary cyst. This report gives such an example.

Womach and Graham[7] have commented upon the association of epithelial hyperplasia in congenital cystic disease of the lung, but in none of their 9 cases was there definite evidence of malignancy. Bass and Singer,[1] in reporting a case of coexisting adenocarcinoma and cystic disease of the lung, described the cysts as being of a bullous rather than congenital type. Though mentioning 2 instances of carcinoma complicating lung cysts, the first, a case of cystic bronchiectasis and the other, a case of bilateral cystic disease, Rogers[6] concluded that the chance of cystic disease of the lung predisposing to bronchial carcinoma is most unlikely.

The above case emphasizes not only the danger in delay but also the hazard inherent in any indeterminate pulmonary nodule, almost half of which we have found to be malignant.[2]

SUMMARY

A case is reported in which serial roentgenograms taken over a 33 month period furnish good proof of the origin of an undifferentiated bronchial carcinoma from a long-standing lung cyst. The implications of this type of lesion are discussed.

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BRONCHIAL CARCINOMA MASQUERADING AS A THIN-WALLED CYST

By J. WINTHROP PEABODY, Jr., M.D.,* EDWARD J. RUPNIK, M.D., *and* JOSEPH M. HANNER, M.D.
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THE rather singular ability of bronchial carcinoma to mimic the roentgenographic manifestations of almost any benign pulmonary lesion is well known. This was not always appreciated, of course, as witness the once prevalent practice of dismissing any unexplained or unresolved pneumonitis as viral in origin, any round circumscribed density as a tuberculoma and any cavitary infiltration as tuberculosis; all lesions in which the malignant potentiality has become adequately documented. However, there remains another disguise behind which a carcinoma can hide, one to which infinitely little attention has been paid, namely, the thin-walled pulmonary cyst. The following case serves to illustrate this point quite well, providing such a striking contrast between its innocent roentgenologic appearance, that of a benign cyst, and its true identity, that of a widely metastasizing carcinoma, that we thought it well worth this case report. As an incidental feature it emphasizes once again how indispensable are previous roentgenograms.

REPORT OF A CASE

The patient, JCN, a forty-nine year old retired non-commissioned officer, was admitted to the United States Naval Hospital, Bethesda, Maryland, on April 11, 1955, for excision of a "bronchogenic cyst" discovered and followed elsewhere since February, 1954. At that time a cystic lesion had been detected in the right mid-lung field in a routine chest roentgenogram, but because he was asymptomatic, the patient refused surgery. In September, 1954, he was admitted to another hospital where staff and consultants alike recommended continued observation of the cyst. Following bronchoscopy at that institution he first began to experience small hemoptyses. These persisted for many months but were unaccompanied by other symptoms. Six months later, because of an increase in the size of the cyst, he was advised to have a thoracotomy.

On admission to this hospital the patient stated that except for a persistent cold he had felt well until three weeks previously, when he began to notice anorexia and a weight loss of fifteen pounds. The hemoptyses had ceased one month prior to admission and he denied any cough, expectoration, dyspnea, wheeze or chest pain. There had been no fever or night-sweats. For the past thirty years he had smoked one package of cigarettes daily. Remainder of the history, including a review of systems, was negative.

At physical examination he was found to be well-nourished and alert, his appearance belying any appreciable weight loss. Significant findings were limited to the chest. The anteroposterior diameter of the rib cage was greater than normal. The lungs were hyper-resonant to percussion. Coarse expiratory rales were audible at the right base posteriorly but cleared on coughing. Breath sounds were comparable bilaterally. There was no palpable lymphadenopathy nor any clubbing of the digits.

Routine laboratory studies were normal. Tuberculin, histoplasmin and coccidioidin skin tests were negative. Chest roentgenograms (Fig. 1) revealed a 10 cm. thin-walled cyst located in the superior segment of the right lower lobe. Comparison with a single postero-anterior roentgenogram taken earlier (Fig. 2) showed a slight increase in size. Previous roentgenograms were not immediately available for comparison, but from the general description of a benign cyst (exact size not stated) it was erroneously presumed that there had been no great change. The tracheobronchial tree appeared normal at bronchoscopy. Pulmonary function studies showed considerable evidence of bronchospasm as manifested by an increment in the maximum breathing capacity from 64.7 liters per minute prior to isuprel administration to 100.9 liters per minute after its use.

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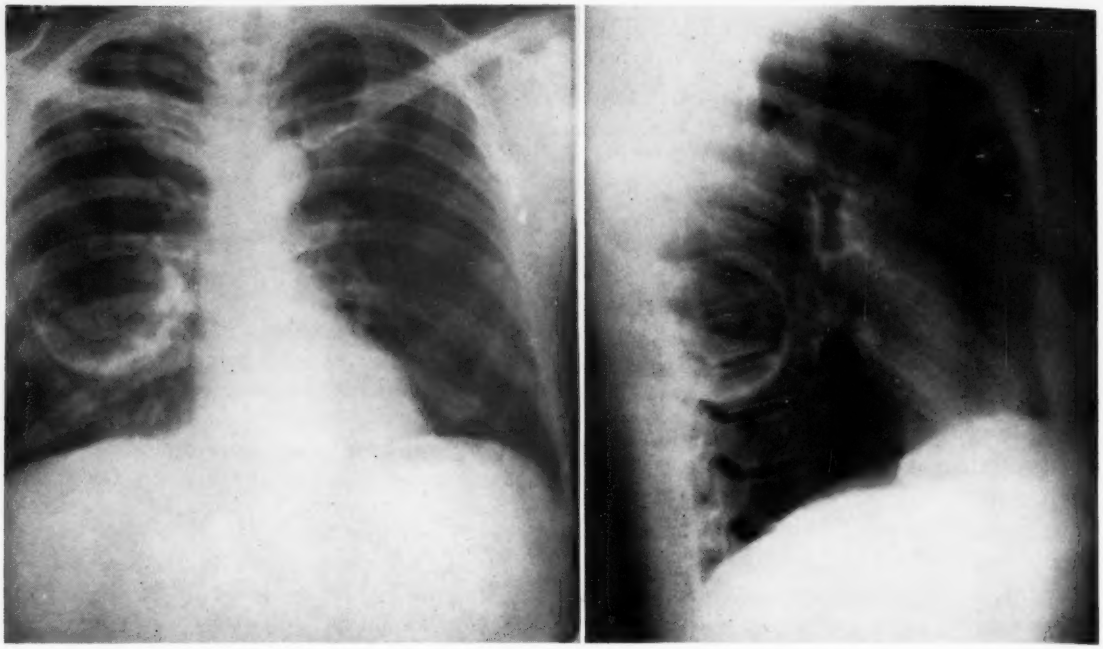

FIG. 1. Posteroanterior and right lateral roentgenograms of the chest showing a smooth, round, thin-walled cyst measuring 10 cm. in diameter located in the superior segment of the right lower lobe. The thickening noted in the medial wall of the cyst was not considered significant until after the microscopic demonstration of epidermoid carcinoma.

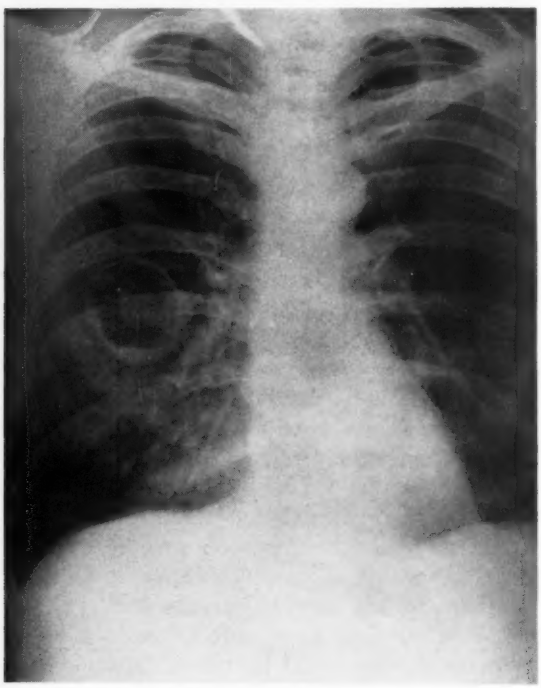

FIG. 2. Posteroanterior roentgenogram three months previously revealing a comparable cystic lesion several centimeters smaller containing a fluid level.

Five sputum specimens were negative for malignant cells.

On April 20, 1955, under endotracheal ether-oxygen anesthesia a free pleural space was entered through the sixth intercostal space. A large thin-walled cyst could be seen and palpated in the apex of the right lower lobe. In the course of resecting the superior segment of the right lower lobe nothing unusual was encountered, the cyst appearing completely benign. Postoperative course was uncomplicated.

Upon opening the cyst the wall was found to be quite thin. The lining showed considerable anthracotic pigmentation but was smooth throughout except for a slightly shaggy surface along one small portion inferiorly. The wall, though not very thick in any portion, was thicker inferiorly than superiorly. Microscopic sections through the wall revealed carcinoma throughout the inferior part of the specimen. The inner surface showed extensive necrosis. The carcinoma cells were large and contained irregular hyperchromatic nuclei and granular eosinophilic cytoplasm. Mitotic figures were prominent, and there was a slight tendency toward gland formation. A large bronchus could

be seen in one section entering the cavity, at which point a ball-valve effect was readily imaginable. The lung surrounding the cyst was slightly compressed and alveolar macrophages were numerous. Pathologic diagnosis: Epidermoid carcinoma, grade 3, with necrosis and cyst formation.

The finding of carcinoma came as a complete surprise, until initial roentgenograms arrived showing the comparatively small size of the lesion when first detected (Fig. 3). After much debate, it was elected to complete the lobectomy. Accordingly, three weeks after the initial procedure the remainder of the right lower lobe was resected. In the course of the dissection a firm fixed unresectable mass was palpated in the subcarinal region. Recovery was uneventful, the patient being discharged two weeks postoperatively. The resected specimen showed no residual carcinoma.

Immediately following discharge he developed pain in the right hip. Inasmuch as this seemed identical to pain that he had experienced nine years earlier, he ignored it. In early July, 1955, the pain increased in severity, necessitating his admission to another hospital where roentgenograms disclosed a fracture through the right acetabulum. He was, therefore, transferred back to Bethesda Naval Hospital for further management.

A bone-survey confirmed the presence of a destructive process in the right acetabulum. Despite a course of deep roentgen therapy (3,200 r) the pain continued. Many subcutaneous metastases appeared. Left hip pain subsequently evolved and repeat roentgenograms showed an additional pathologic fracture through the superior ramus of the left pubis. Several courses of nitrogen mustard (methyl bis [B-chloroethyl] amine hydrochloride) were given without significant benefit. Finally, because of intractable pain he was placed on cortisone, 50 mg. twice daily. Great subjective improvement promptly ensued. Nevertheless, he progressively deteriorated, though remaining relatively pain-free due to steroid therapy.

On October 30, 1955, he suddenly became comatose and expired. Permission for autopsy was denied.

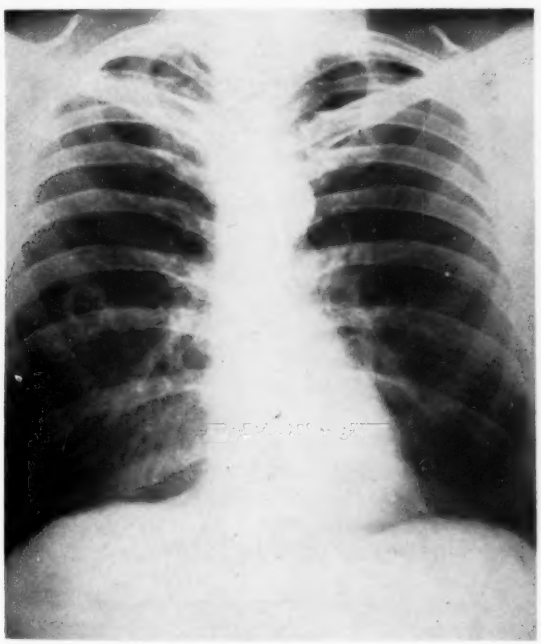

Fig. 3. Posteroanterior chest roentgenogram taken fourteen months prior to operation showing the cyst when initially detected. Although the increase in size is suggestive of malignancy, neither this film nor an accurate report were available preoperatively.

DISCUSSION

Cavitation within bronchial carcinomas is not uncommon. As emphasized by Liebow,[5] the cell type is invariably epidermoid some 20 per cent of which form cavities greater than 4 cm. in diameter by the time they come to necropsy. In such instances the walls are characteristically thick and nodular, but the roentgenographic appearance may sometimes simulate a lung abscess or tuberculous cavity quite closely. While the clinical picture usually provides a helpful guide as to etiology, the similarity may at times be practically identical so that even at operation careful attention must be paid to such seemingly insignificant details as the presence of extensive anthracotic pigmentation in the wall of a cyst, a finding more suggestive of carcinoma.[5] The thinner and less nodular the wall of the cavity, the greater will be the diagnostic difficulty. However, for an excavative carcinoma to resemble a smooth, spherical, thin-walled cyst must be an exceedingly rare occurrence. For one to grow uniformly and symmetrically in all directions seems most unlikely; for the relatively rigid walls of a

once solid carcinoma to balloon up would appear impossible under any circumstances. Hence, we seriously question a purely excavative mechanism.

Certainly, in this case there was a different modus operandi. True, there was evidence of extensive tumor necrosis along the inner surface of the cyst, but the roentgenographic evolution of the lesion with its rapid increase from a small to a large thin-walled cyst, all the while maintaining a perfectly smooth round contour, provides almost incontestable evidence of an origin like that of any tension-type cavity, that is, regional obstructive emphysema due in this instance to neoplasm. Fluid retention as seen on one roentgenogram (Fig. 2) is another indication of an obstructive element, and this is further supported by microscopic study of the bronchocavitary junction. While regional obstructive emphysema secondary to carcinoma is not too uncommon, it is most unusual for it to produce a lesion resembling the one presented here. Anderson and Pierce,[1] for example, have analyzed 6 cases of cystic bronchial carcinoma, all more irregular than ours, for which they postulate a valvular-obstructive origin.

There should be no need to point out that this is assuredly not an example of a carcinoma arising in a congenital cyst, a mode of origin not generally appreciated though championed and well documented by Korol.[2,3] Having denied the applicability of a similar etiology in our case, we feel compelled to comment upon the report of Larkin and Phillips[4] whose case, both in roentgenographic evolution and clinical course, showed a remarkable parallelism to our own, yet is reported as an instance of a carcinoma originating in a pre-existing cyst. Granting that in their case the tumor was confined to but one part of the cyst wall, the initial size, time of appearance, and location of the cyst hardly support a congenital origin. To us it seems more plausible that the cyst resulted from, rather than antedated the carcinoma, arising, we suspect, from check-valve endobronchial obstruction. As in our case, theirs too illustrates how the presence of an underlying malignancy may be overlooked even with the specimen in one's hand. In our case, had earlier roentgenograms been obtained prior to surgery, our index of suspicion would undoubtedly have been greater, but rapid enlargement or not, a case like this provides a dramatic demonstration of the need for considerable discrecretion in assaying the significance of any thin-walled pulmonary cyst.

SUMMARY

A case is presented in which a bronchial carcinoma mimicked the roentgenographic, clinical and even the operative picture of a thin-walled bronchogenic cyst. The origin of cavitative and cystic changes secondary to carcinoma of the lung is discussed with particular emphasis upon the importance of regional obstructive emphysema. Attention in called to the hazard in dismissing every cystic pulmonary lesion as benign.

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PULMONARY OIL EMBOLISM*

A COMPLICATION OF HYSTEROSALPINGOGRAPHY

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INTRAVASATION of the radiopaque medium during hysterosalpingography has been reported in a number of papers in the literature.[3,5,7,8,11,12] Very few reports have demonstrated the presence of findings in the chest roentgenogram accompanying this complication. The following case is reported to indicate the presence and innocuous course of pulmonary oil embolism.

REPORT OF A CASE

M.E., a twenty-six year old married Negro female, gravida 3, para 1, was admitted to the hospital on April 11, 1955, because of vaginal bleeding of three weeks' duration. The past menstrual history was unremarkable and her last menstrual period had occurred on March 9, 1955.

On examination, the cervix was soft and patulous. No bleeding was noted. The uterus was somewhat enlarged. An Aschheim-Zondek test was negative.

A hysterogram was made on April 13, 1955. The preliminary scout film disclosed a cluster of calcific densities in the region of the uterus consistent with a calcified fibroid. Some bleeding was noted from the cervical os. Roentgenograms obtained after the injection of lipiodol by means of controlled manual pressure showed the presence of a filling defect along the left side of an enlarged uterine cavity. It was felt that this might represent an additional fibroid. A bizarre distribution of lipiodol was observed surrounding the uterus, characterized by streaks and droplets of a vascular pattern (Fig. 1). The patient experienced no untoward reaction from the procedure. On April 15, 1955, a dilatation and curettage was performed. Examination of the material obtained showed the presence of necrotic and degenerating placental tissue.

A roentgenogram of the chest on April 18, 1955 (Fig. 2) showed a diffuse, almost granular, submiliary, confluent distribution of metallic opacities, scattered mostly through the upper two-thirds of both lungs and confined to the posterior segments. This localization of contrast medium was attributed to the fact that hysterography had been carried out with the patient in the supine position. The patient was followed with interval chest roentgenograms through August 20, 1955. There was no evidence of opaque oil in the roentgenogram of June 11, 1955, or in a subsequent one (Fig. 3).

FIG. 1. Roentgenogram of the pelvis immediately after hysterosalpingography. Note the streaking of opaque medium (lipiodol) in the pelvis. These opaque tracts represent the venous drainage of the uterus.

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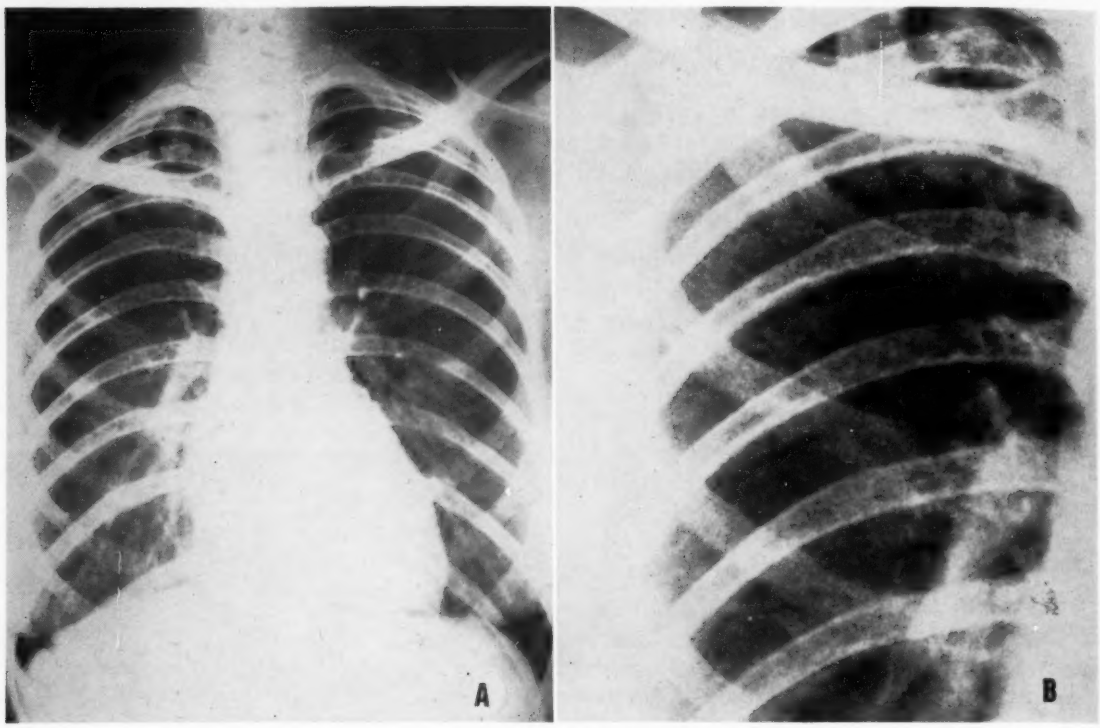

FIG. 2. (*A*) Posteroanterior roentgenogram of the chest, five days following hysterosalpingography. Note the old tuberculous infiltration in the right apex which has been proved stable in the serial examinations. The roentgen findings of pulmonary oil embolism, though clearly apparent in the original roentgenogram, do not stand out in the reproduction. (*B*) Magnified "blow-up" of the right lung from *A*. There is diffuse distribution of metallic, granular and submiliary opacities concentrated in the upper portion of the lung.

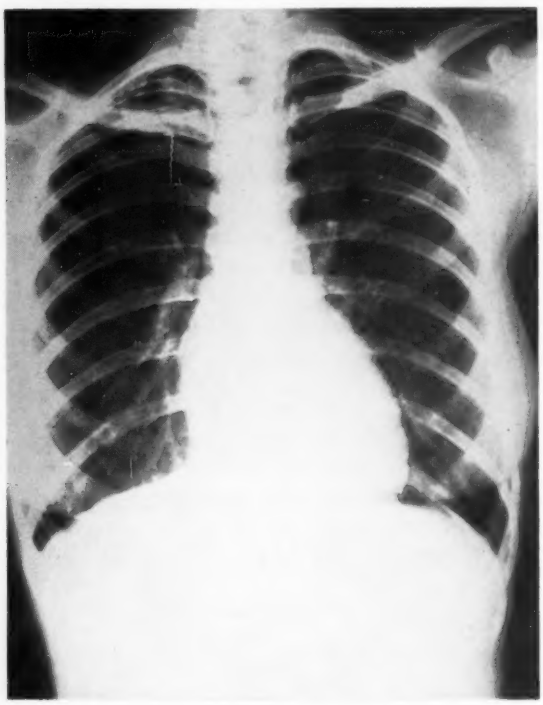

FIG. 3. Posteroanterior roentgenogram of the chest two months following hysterosalpingography. There is no evidence of opaque oil in the lungs. The right apical infiltration is unchanged.

DISCUSSION

Following the introduction of lipiodol as a contrast medium in diagnostic roentgenology, Sicard and Forestier[9] carried out investigative studies on the reactions of animals and then human beings to intravenous injections of this substance. In the humans, the lipiodol reached the lung in 5–6 seconds and then disappeared suddenly after remaining 6–8 minutes in the lungs. The patient's only objective sign was a slight cough.

Walther[10] noted in a similar experiment with rabbits that practically all of the lipiodol was concentrated in the smaller veins and capillaries of the lungs. Most of the lipiodol, he observed, is broken up

into its two constituents, iodine and fat, by the blood lipases and the lipolytic action of lung tissue. The urine serves as the route of excretion for most of the iodine, appearing as potassium iodide during the first eight days. The fat is saponified and carried off by the circulation. Some of the lipiodol is engulfed by phagocytes from the vascular endothelium and adventitial cells and by the alveolar epithelium.

Usually, no significant reactions have been reported in the literature following the intravasation of lipiodol during hysterosalpingography. Cough, blood-tinged sputum, chills and fever have been recorded.[3,12]

On the other hand, death of a sixty year old female is reported by Gajzágó[4] following this complication. Autopsy disclosed oil emboli in the lungs, heart and kidneys. Walther[10] warns that septic embolization may occur in instances when bacteria accompany the lipiodol into the lungs, during hysterosalpingography.

The indications for the performance of hysterosalpingography have been well documented in a number of reports.[3,5,7] The occurrence of intravasation of the medium has been considered to be due to: (1) trauma induced during the procedure; (2) use of excessive pressure during injection; (3) presence of hypervascularity or thin-walled sinuses in the cervical canal or uterine cavity such as in recent menses, recent dilatation and curettage and intrauterine pregnancy; (4) use of less viscous water-soluble media. In a series of 2,500 hysterosalpingographies reported by Marshak, *et al.*[7] no case of intravasation occurred with the use of lipiodol, but in 38 cases intravasation occurred when a water-soluble substance had been used.

Although pulmonary embolization is usually an innocuous complication, it should be avoided if possible. Hysterosalpingography should not be carried out in the presence of a known intrauterine pregnancy, pelvic inflammatory disease with a purulent vaginal discharge or, probably, in instances of recent active uterine bleeding.

When performed, hysterosalpingography is best carried out about eight days after completion of the menstrual period. A similar delay must be allowed following a dilatation and curettage examination. The procedure should be done with little manual pressure and fractional injections of small quantities of radiopaque substance. In this respect, water-soluble media might be considered more suitable. Fluoroscopy has also been used to control the injection.[1] A short, blunt tipped or soft flexible tipped cannula should be used with avoidance of trauma at its insertion.

ROENTGEN ASPECTS

With the occurrence of the intravasation of the contrast medium, immediate roentgenograms of the abdomen usually outline the uterine plexus, and the uterine and ovarian veins. When embolism of the lungs develops, the appearance is frequently that of diffusely and evenly distributed nodular densities about 1–3 mm. in diameter. If an oily substance is used, these densities have the roentgen appearance of opaque oil droplets.[2,9] Linear and patchy infiltrates have been noted suggesting small pulmonary vessels and infarcts, respectively.[5,6] Some have interpreted these infiltrates as representing zones of perifocal pneumonitis.[2] Pleural fluid may accumulate. In those instances in which intravasation occurs while the patient is in a horizontal position, the pulmonary distribution may be more concentrated in either the posterior or anterior portion of the lungs depending upon whether the patient was in the supine or prone position when the incident occurred.

Radiopaque material visualized in the lungs sometime after the immediate episode may be contained within phagocytes.

With the knowledge of previous hysterosalpingography and, additionally, the detection of intravasation in the abdomen, the pulmonary manifestations of the accident should present no problem in the differential diagnosis. When lipiodol has been used, its roentgen appearance is

usually characteristic; however, when less opaque water-soluble contrast media are employed, the differential diagnosis should also include the various miliary diseases of the lungs. The rapid disappearance of pulmonary findings, in association with the well-being of the patient, should suggest the correct diagnosis. The fact that a hysterography had been performed previously will then clarify the situation.

CONCLUSION

A case of pulmonary oil embolism complicating hysterosalpingography is presented. The pathologic mechanism is discussed and suggestions for avoiding this complication are submitted.

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UNUSUAL PULMONARY CHANGES SECONDARY TO CHEST TRAUMA*

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PULMONARY changes, seen in the chest roentgenogram and at autopsy following varying degrees of trauma to the chest, have been known and recorded for some time.[2,3,9,16,17] Such changes may be secondary to blast injuries, both in air and in water, high velocity missiles wounding the chest wall, and particularly high velocity injuries secondary to automobile and aircraft accidents. For the most part, the ensuing roentgenographic changes have been recorded as areas of consolidation, varying in extent according to the location and area of the injury. This consolidation may involve portions of pulmonary segments, an entire lobe, or an entire lung on one or both sides. Usually these areas of consolidation disappear fairly rapidly, *i.e.*, in a period of six to ten days, occasionally appearing and disappearing in forty-eight hours in patients with lesser trauma.

DeTakats, Fenn and Jenkinson,[5] and Daniel and Cate[4] each produced areas of consolidation in the lung opposite to the injured one in experimental animals and postulate a reflex mechanism in part responsible for some of the large areas of consolidation or contrecoup type consolidations sometimes seen with chest trauma. They further postulate that pulmonary consolidation secondary to upper abdominal operative procedures may be initiated by such reflexes. DeTakats, *et al.* found that areas of traumatic atelectasis occurred in 86 per cent of a series of patients with fractured ribs and in 65 per cent of patients seen with chest trauma and no fractured ribs.

The group of patients recorded in the present report all suffered rather severe, nonpenetrating chest wall injuries with resultant areas of pulmonary consolidation. The unusual feature in each patient was the development of varying sized air-filled cavities within the pulmonary consolidations.

These cavities were both unilocular and multilocular, centrally and eccentrically placed and resembled the type of "pneumatocele" formation seen particularly in children secondary to clearing lobar pneumonias. The time of appearance of the cavity or pneumatocele may be immediate, within a few hours, or delayed for several days. Patients in whom such cavities appeared usually had a more prolonged time interval before the chest roentgenogram completely cleared than those without such cavities. This may be related to the severity of the chest trauma, although this conclusion is not at all certain. It is extremely important to recognize that such air-filled cystic spaces can form and that they are not tuberculous in nature, do not represent lung abscesses and that they will completely clear within a relatively short period of time with no residual sequelae and with little treatment other than symptomatic. Bronchoscopy and antibiotics seemed to produce no more rapid clearing than in those patients in whom such procedures were not used. The minimum time of clearing was ten days and the maximum time three months. Contusions without pneumatocele formation or extensive fractures cleared in three days to three weeks. We have no experience of the effect of intercostal nerve blocks in this small group of patients with pneumatoceles, but in other patients with similar consolidations and no pneumatocele formation when intercostal blocks were used, there was no decrease in the time necessary for clearing of the consolidated areas.

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Pulmonary contusions with pneumatocele formation are much more frequent in roentgenologic practices which include examinations of many traumatic injuries. Because of the benign nature of these contusions, pathologic material is not usually obtained; however, in one patient of the group here presented, the pulmonary symptoms and roentgen changes were so severe and prolonged, it was thought best to remove his right lower lobe. In this instance, as reported by others, extravasations of blood were found in interstitial spaces, alveoli and bronchi. In addition, transudation of fluid was found in interstitial spaces and may be secondary to the irritating effect of the blood possibly increasing bronchospasm and exudation of fluid into alveolar and interstitial spaces.[16]

REPORT OF CASES

CASE I. D.L., a six year old old white female, fell from a horse and sustained multiple rib fractures. Roentgenograms made two hours after the injury (Fig. 1) revealed fractures of the third and fourth ribs in the right anterior axillary line and an area of increased density in the right mid-lung field containing an air-filled cyst-like lesion. There was no evidence of pneumothorax and no evidence of pleural fluid.

Subsequent roentgenograms made in 24 hours and 48 hours revealed a more sharply defined area of consolidation. In addition, the air space with complete absence of pulmonary markings had increased somewhat in size. Ten days following the injury there was a decrease in size of the apparent pulmonary consolidation. At this time a smaller cystic area was still visible. At three months both lungs were completely clear (Fig. 2).

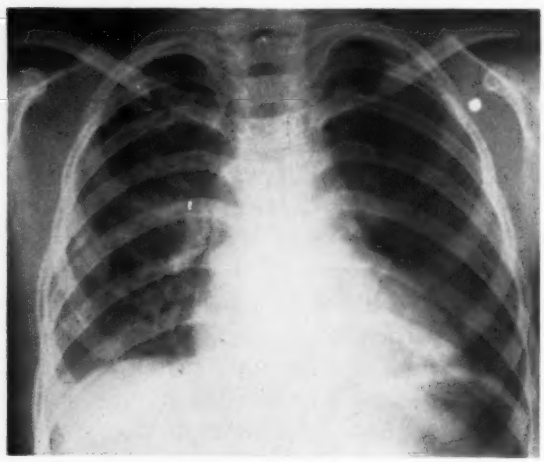

FIG. 1. Case I. Fractures of the anterior portions of the right third and fourth ribs. "Pneumatocele" within an area of consolidation in the right middle lobe.

FIG. 2. Case I. Three months later complete clearing of the right middle lobe lesion. Healed rib fractures.

Because of the area of consolidation within which appeared an apparent cavity, this child was extensively studied for the presence of tuberculosis. All studies including guinea pig inoculation were negative for acid fast bacilli.

CASE II. A nineteen year old white boy suffered a bruise of the left side of his chest in an automobile accident.

Roentgenograms made within several hours of the injury (Fig. 3) revealed a pneumothorax on the left side with approximately a 10 per cent collapse of the lung and an indistinctly outlined, cloudy area in the left upper lobe. Within this clouded area were several air-filled spaces.

One week following the injury the area of consolidation was more sharply outlined and lobar in distribution, extending out to the pleura.

The several cystic areas were also somewhat larger and more sharply circumscribed. At this time a roentgenogram made approximately one year previous to the injury was available, and this revealed completely negative chest findings.

Subsequent roentgenograms made at weekly intervals showed gradual regression of the area of consolidation. The patient was completely

Fig. 3. Case II. Left sided pneumothorax with an irregular area of consolidation in the left upper lobe within which are multiple cystic air-filled cavities.

asymptomatic three weeks after the injury. After five weeks he developed a low grade fever and brought up a moderate amount of sputum. At this time there was some increase in the consolidation and some air and fluid levels appeared in the cyst-like lesions. At the end of approximately eight weeks following the injury, the lesion had completely resolved (Fig. 4) and the chest remained normal in subsequent follow-up examinations.

Case III. D.C., a sixteen year old white girl, suffered a head injury and a contusion to the chest wall in an automobile accident. She was first treated at another hospital where she apparently had a two day period of unconsciousness. Two weeks following the initial injury she was admitted to the University Hospital for a study of a possible subdural hematoma. At that time she was still mentally clouded and the physical examination revealed a right hemiplegia. The chest roentgenogram showed a sharply outlined lobular consolidation in the lower portion of the right lower lobe. Within this area of consolidation, several cyst-like cavities were demonstrated. No rib fractures were identified. Investigation for the presence of a subdural hematoma disclosed no evidence of such. She remained in the hospital approximately two weeks during which time she had no cough or fever. Her tuberculin test was negative and gastric washings were negative for acid fast bacilli.

Subsequent roentgenograms showed gradual clearing of the area of consolidation and gradual disappearance of the cystic areas. Follow-up examinations made at three, five and eighteen months revealed completely normal chest roentgenograms in a patient who was asymptomatic.

Case IV. This twenty-one year old white man was in an autombile accident in which his chest struck the steering wheel of the car he was driving. Following the accident he was momentarily unconscious. At the time of the admission to the hospital, his main complaint was rather severe pain over the entire right side of the chest. Other than this he was asymptomatic. His past history was noncontributory.

On physical examination there was a bruise over the anterior portion of his chest and some pain on pressure anteriorly and laterally. There were some dullness and distant breath sounds over the lower one-half of the right hemithorax posteriorly. The remainder of the physical examination disclosed no abnormal findings. The laboratory examinations revealed a white blood cell count of 18,000, hemoglobin of 13 gm. and a normal urine.

The initial roentgenogram of the chest (Fig.

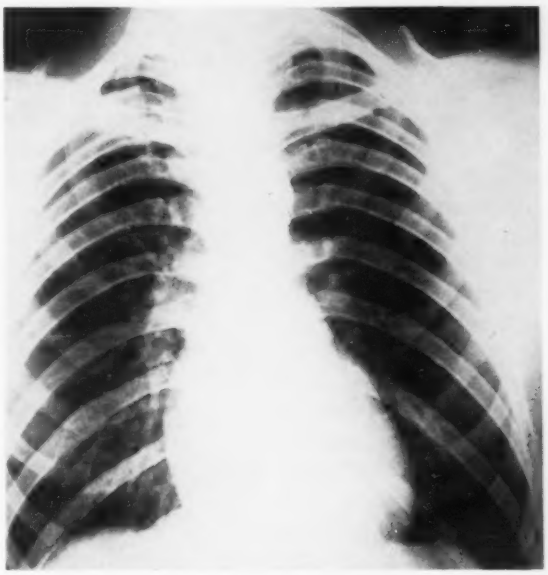

Fig. 4. Case II. Roentgenogram made eight weeks later showing complete clearing of the left upper lobe lesion and disappearance of the pneumothorax.

FIG. 5. Case IV. Large thick walled cavity with an air fluid level within a sharply circumscribed area of consolidation in the right lower lobe. This cleared completely in three months.

5) demonstrated a sharply circumscribed area of consolidation in a major portion of the right lower lobe. There were no rib fractures and the remainder of the chest was clear. Subsequent roentgenograms three days later showed a thick walled, multiloculated cavity containing several fluid levels within the area of consolidation in the right lower lobe. This remained essentially unchanged for the next two weeks.

Seventeen days after the injury, the patient developed some added respiratory distress and a right thoracentesis was done with removal of a small amount of serohemorrhagic fluid. Following this procedure and with no change in the roentgen appearance of the chest, the patient developed a septic type temperature and it was felt necessary to perform a thoracotomy. The right hemithorax was operated on with resection of a portion of the tenth rib, the periosteal bed and a segment of underlying pleura. This permitted entrance into the large cavity in the right lower lobe. Digital exploration and inspection of the interior of the cavity revealed about 100 cc. of brick red, purulent, sanguinous fluid. The fluid was aspirated and a portion of the shaggy wall of the cavity removed for histologic study.

Microscopic examination revealed extensive old hemorrhage with hematoma of the pleura and adjacent lung parenchyma, resulting in partial organization and fibrosis. There was chronic pneumonitis associated with fibrosis in the relatively less involved pulmonary parenchyma. The cavity was drained and it healed uneventfully.

The man returned to full activity ten weeks after his initial injury. His final roentgenogram revealed only several linear fibrotic strands in the right lower lobe.

CASE V. This twenty-two year old white man was admitted to the hospital with a history of being caught by the closing canopy of an F-9-F-5 airplane causing injury to his chest and left arm. Subsequent to the injury he fainted and was found by a fellow worker. At this time, he was quite pale, sweating and having some shortness of breath. Immediate treatment was instituted with administration of oxygen and morphine, following which he was sent to the hospital.

His past history was unremarkable except for some hematuria in June, 1952. Upon admission to the hospital the patient's main complaint was pain and cough on deep breathing.

Physical examination disclosed some tender abrasions and contusions across the anterior and posterior aspects of the upper portions of the

right side of the chest. Expansion was symmetrical bilaterally. Breath sounds were diminished over the mid portions of the chest both anteriorly and posteriorly. There was some hyperresonance to percussion. Laboratory examination revealed a white blood cell count of 22,500, a hemoglobin of 14 per cent and a normal differential count.

Roentgenograms of the chest made approximately three hours after the injury showed an irregular area of consolidation in the anterior segment of the right upper lobe near the hilum. The remainder of the chest revealed nothing abnormal. There were no rib or vertebral fractures.

The patient was treated conservatively with aspirin and codeine and antibiotics. The clinical course was then uneventful. On about the sixth day after admission the patient coughed up a small amount of an apparently well organized blood clot. Subsequent roentgenograms of the chest demonstrated no appreciable change in the size or shape of the area of consolidation in the right upper lobe, but there were multiple varied sized cystic cavities within the consolidation (Fig. 6). Repeated roentgenograms made during the next three weeks showed gradual disappearance of the consolidation and cystic areas. Six weeks after the injury the patient had a normal appearing chest roentgenogram and was returned to full activity.

Case vi. E.M., a twenty-three year old white man, was in an automobile accident in which he suffered a head and chest injury. At the time of entry into the hospital, he was somewhat irrational. There were multiple small abrasions and scratches about the face and some bleeding from the left ear. The pupils reacted equally and there was a slow strabismus of the left eye with lateral gaze. In addition there was some questionable weakness of the entire left side. There were also multiple gross skin abrasions over both arms and the anterior chest wall on the right side. The positive laboratory findings were limited to a two plus blood in the urine on the initial examination with gradual clearing. No gross kidney or bladder lesions were present. Roentgenograms of the skull revealed a left temporal skull fracture extending across the squamous portion of the temporal bone. In addition there was clouding of the mastoid

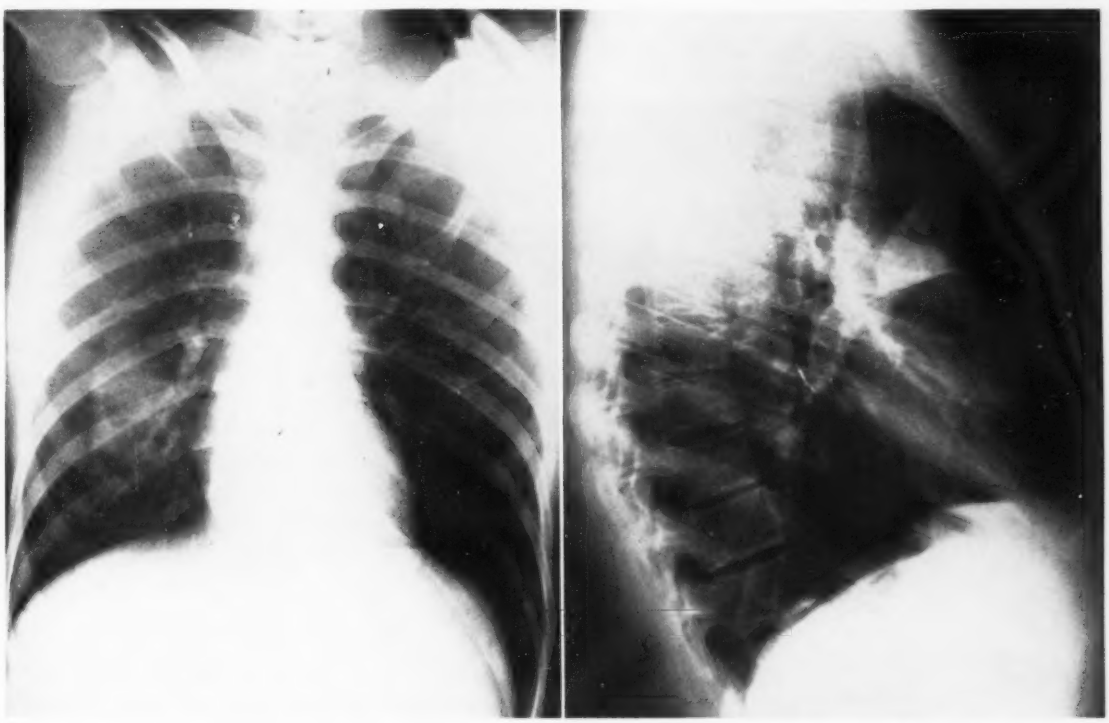

Fig. 6. Case v. Roentgenograms made six days after injury showing several sharply circumscribed areas of consolidation in the right upper and lower lobes with multiple varied sized cystic cavities within the consolidation. No sequelae were present six weeks later.

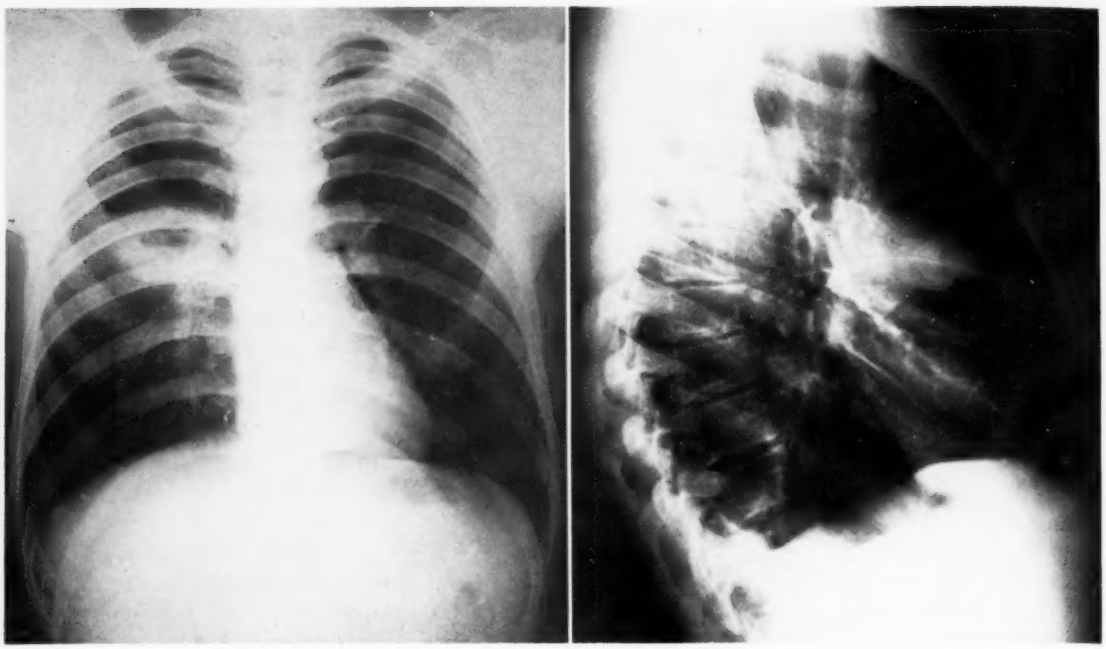

FIG. 7. Case VI. Roentgenograms made two days after injury showing a sharply circumscribed area of consolidation in the anterior segment of the right upper lobe within which are several cystic cavities.

cells on the left side; however, a fracture line could not be identified. The chest roentgenograms were made with the patient supine and showed a fairly sharply circumscribed area of consolidation in the right upper lobe. In addition, there was thought to be a fracture of the anterior portion of the right fifth rib with no displacement of the fragments. Subsequent roentgenograms of the chest revealed no appreciable change in the size of the consolidation in the right upper lobe, but within two days multiple, varied sized cystic spaces appeared within the area of consolidation (Fig. 7). These were characteristic of previous "pneumatoceles" demonstrated in the other similar injuries. On the fourth hospital day the otorrhea from the left ear stopped, and by this time the patient was perfectly rational and cooperative. His chest pain and neurologic findings gradually cleared over the next several weeks, and he was returned to full activity six weeks after his injury. The final roentgenogram of the chest at the time of his discharge from the hospital (Fig. 8) and subquent roentgenograms have all revealed no abnormal findings.

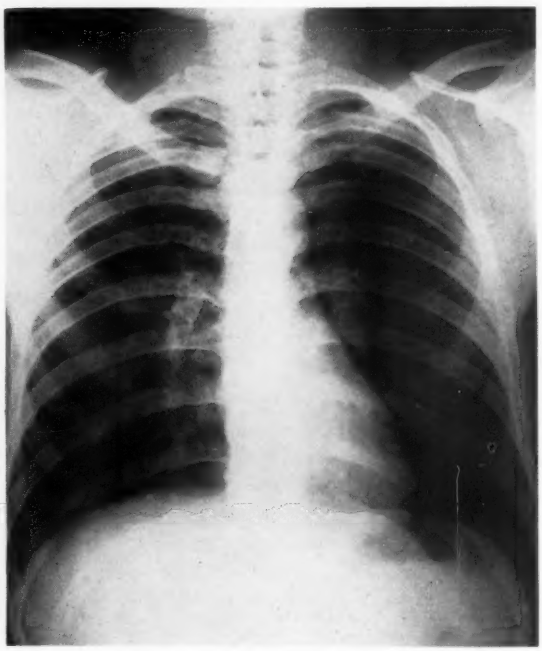

FIG. 8. Case VI. Six weeks after injury no visible abnormalities remaining.

SUMMARY

1. Varying degrees of chest trauma with or without rib fractures may produce pulmonary consolidations of varying size. In certain patients subsequent rounded cyst-like cavities develop and disappear without further therapy.

2. Such cavities should not be confused with tuberculous or other granulomatous cavity producing diseases.

3. Six case reports are presented.

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ROENTGENOGRAPHIC DETECTION OF MINIMAL PNEUMOTHORAX IN THE LATERAL DECUBITUS POSITION*

COSTOPHRENIC SINUS SIGN

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THE lateral decubitus position has long been useful in the roentgenographic examination of the abdomen and chest. The particular value of this position lies in its ability to demonstrate shifts of fluid and gas. We have found it helpful in the detection or confirmation of the presence of a pneumothorax.

In the upright position, the free pleural air of a pneumothorax distributes itself as a mantle over the upper parts of the partially collapsed lung. The diagnosis is based upon the demonstration of the fine line caused by the visceral pleura after its separation from the parietal layer. There is a complete absence of lung markings between the two pleural layers. Unfortunately, a small pneumothorax may escape detection despite a diligent search for pleural separation. On upright films, evidence of a small pneumothorax must be searched for in the apical portion of the lung field. In this region the first three ribs, clavicle and scapula tend to obscure the pulmonary shadows. Furthermore, the pulmonary markings are normally sparse in this peripheral area of the lung. Some patients, because of pain or general weakness, may be unable to stand or sit for upright roentgenograms. Finally, mobile and other roentgen equipment making use of a large focal spot or requiring long time exposures may not give fine enough detail to visualize the fine line of the detached visceral pleura.

A diagram of the chest sectioned in the coronal plane shows the relationship of the parietal pleural reflections to the lung (Fig. 1*a*). The lowest pleural reflection, (lowest point of the costophrenic sinus), is at the mid-axillary line and reaches to the tenth rib or tenth intercostal space. The lung also extends farthest downward laterally, but even in deepest inspiration falls considerably short of the bottom of the costophrenic sinus. Thus, the costal and diaphragmatic parietal pleurae are here in contact during all phases of respiration and most of the costophrenic sinus is roentgenographically invisible.

A diagram of the chest, representing a coronal section of a hemithorax in the lateral decubitus position, again shows that the only part of the costophrenic sinus that is roentgenographically visible is that part containing lung (Fig. 1*b*). When free air is present, it will ascend to the uppermost portion of the pleural cavity, which, in the lateral decubitus position, is the costophrenic sinus (Fig. 1*c*). In pneumothorax, the costophrenic sinus is seen as a distinct, bulging, air-filled sac extending much farther caudad than the lung (*costophrenic sinus sign*). The lung and its visceral pleural line project into the cranial portion of this sac.

Roentgenograms made in the lateral decubitus position, utilizing a horizontal ray, have demonstrated otherwise undetected cases of pneumothorax; in other instances, such films have made definitive a previously doubtful diagnosis. The shape of the air-filled costophrenic sinus is very characteristic and constitutes a helpful sign in the diagnosis of pneumothorax. In addition, the free air above the costophrenic sinus is more clearly seen against the lateral chest wall than it is in the apical area on upright films. This is because the visceral pleural line crosses, not parallels, the ribs. The patient lies on his unaffected side with

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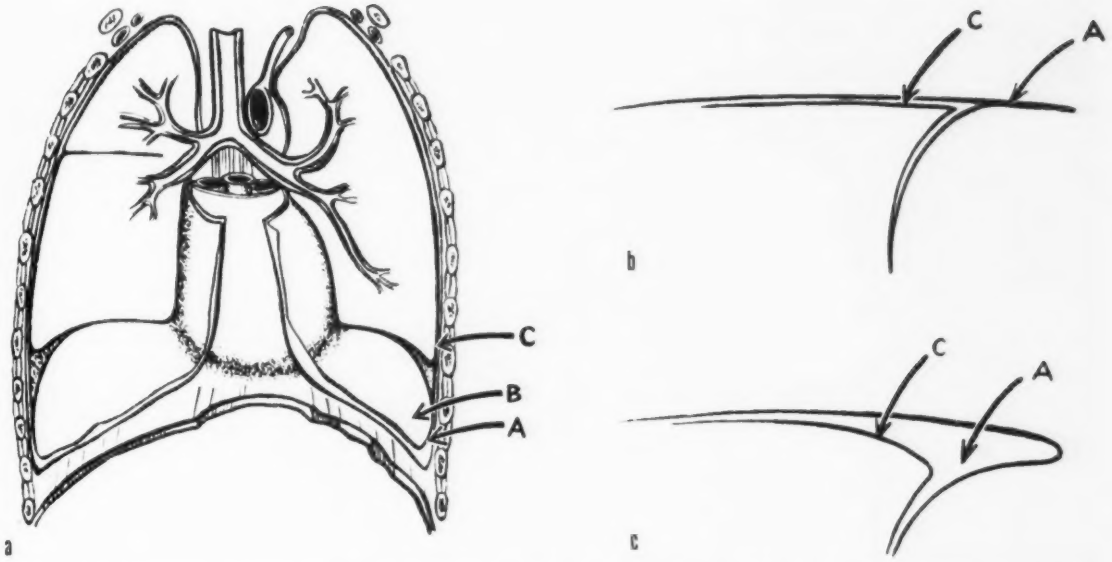

Fig. 1. (*a*) Diagram of chest sectioned through the coronal plane showing the caudal extent of costophrenic sinus (A). Note that the lowermost lung margin (C) is well above the bottom of the sinus. The diaphragmatic parietal pleura (B) and costal pleura form a potential space. (*b*) Normal hemithorax in the lateral decubitus position showing that the diaphragmatic and costal pleural surfaces are normally in contact in the costophrenic sinus (A). Sinus is thus not visible on roentgenogram. (*c*) *Costophrenic sinus sign* of pneumothorax. The free pleural air balloons out the space between the diaphragmatic and costal pleurae (A). The lung (C) projects only part way into this air sac.

enough padding placed under the lower ribs to insure proper elevation of the region of the costophrenic sinus. The exposure is made during expiration.

The following two cases have been selected to illustrate the aid that may be obtained from lateral decubitus films in the diagnosis of small pneumothoraces.

REPORT OF CASES

Case I. This young woman had a history of recent chest trauma incurred during an automobile accident. A posteroanterior chest film (Fig. 2*a*) showed several fractures of the ribs of the left hemithorax but no definite evidence of pleural separation. Because of abdominal pain, films of the abdomen, including a lateral decubitus view, were obtained. This latter film disclosed a large, air-filled, bulging costophrenic sinus with the lung margin clearly outlined (Fig. 2*b*). The extent of this air pocket is considerably more caudad than the lung normally reaches. Several days later, after absorption of the free pleural air, the lateral decubitus film showed a costophrenic angle of normal size and depth (Fig. 2*c*).

Case II. This young girl had been stabbed in the right chest. A posteroanterior chest film showed only a "high" right diaphragm; no evidence of pneumothorax (Fig. 3*a*). The lateral decubitus film clearly showed the *costophrenic sinus sign* of pneumothorax (Fig. 3*b*) as well as fluid levels. The "high" diaphragm was really infrapulmonary fluid (blood).

DISCUSSION

Roentgenographic examination of patients with a history of chest trauma, or possible pneumothorax from other causes, should include a lateral decubitus view of the lower chest. In the absence of an adhesive pleuritis, the costophrenic sinus will balloon out with air and present the characteristic *costophrenic sinus sign*. Even when sufficient pleuritis is present to seal the sinus, the free air will be clearly seen against the lateral chest wall.

An attempt was made to compare the roentgenologic appearance of known small amounts of free pleural air in the upright posteroanterior and lateral decubitus pro-

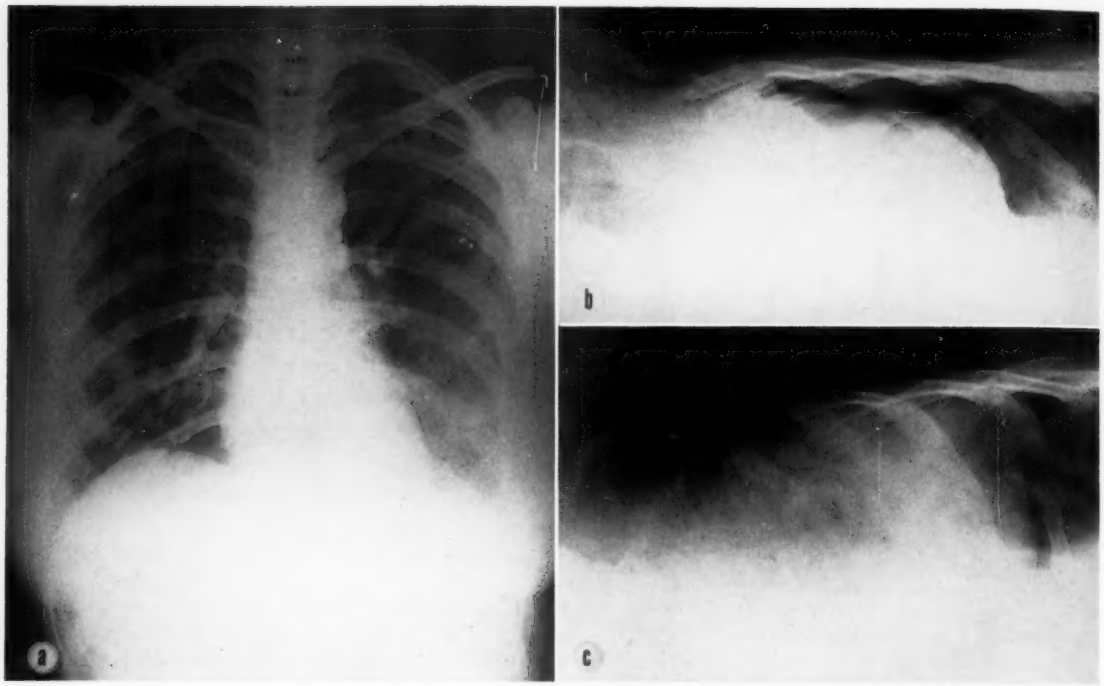

FIG. 2. Case I. (*a*) Posteroanterior roentgenogram showing chest in expiration. Fractured ribs present in left axillary line. Definite evidence of pneumothorax is not seen. (*b*) Cut-out of lateral decubitus film of abdomen. *Costophrenic sinus sign present.* Note caudal extent of sinus. Visceral pleural line retouched for reproduction but clearly seen on original film. (*c*) Lateral decubitus film after absorption of free pleural air; normal costophrenic angle.

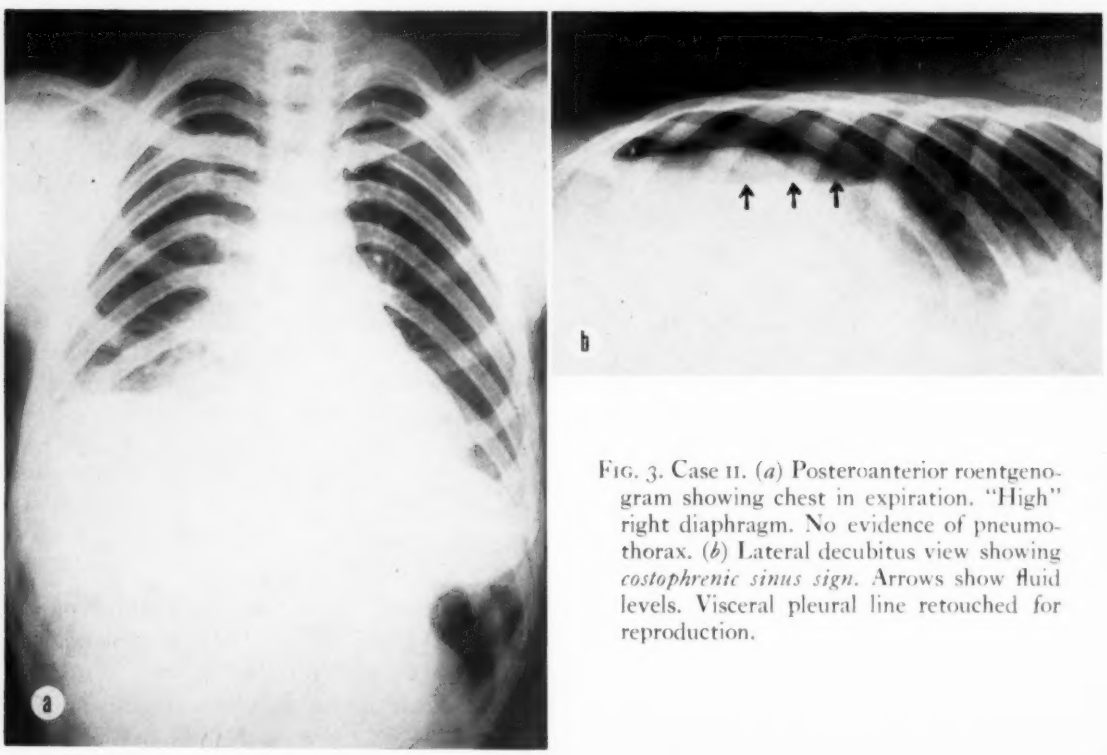

FIG. 3. Case II. (*a*) Posteroanterior roentgenogram showing chest in expiration. "High" right diaphragm. No evidence of pneumothorax. (*b*) Lateral decubitus view showing *costophrenic sinus sign.* Arrows show fluid levels. Visceral pleural line retouched for reproduction.

jections. Exactly 50 cc. of air was injected into the right pleural cavity of an elderly female in cardiac failure during a thoracentesis. The upright inspiratory and expiratory roentgenograms showed no detectable evidence of pneumothorax. The lateral decubitus film (Fig. 4*a*) showed free air in a deformed costophrenic sinus with a definite fluid level. In another patient, 100 cc. of air was injected. This time several different interspaces were used during the removal of fluid because of the inability to obtain sufficient fluid at any single site; some bleeding also occurred. Chest roentgenograms made immediately afterwards showed the pneumothorax in both the upright and lateral decubitus positions. The *costophrenic sinus sign* was not present (Fig. 4*b*); its absence was probably due to an adhesive pleuritis which had sealed the costophrenic sinus and had also interfered with the removal of fluid. However, the free air was still more readily detected on the lateral decubitus view than on the upright posteroanterior film because the visceral pleural line is at right angles to the curve of the ribs.

The lateral decubitus view is easy to

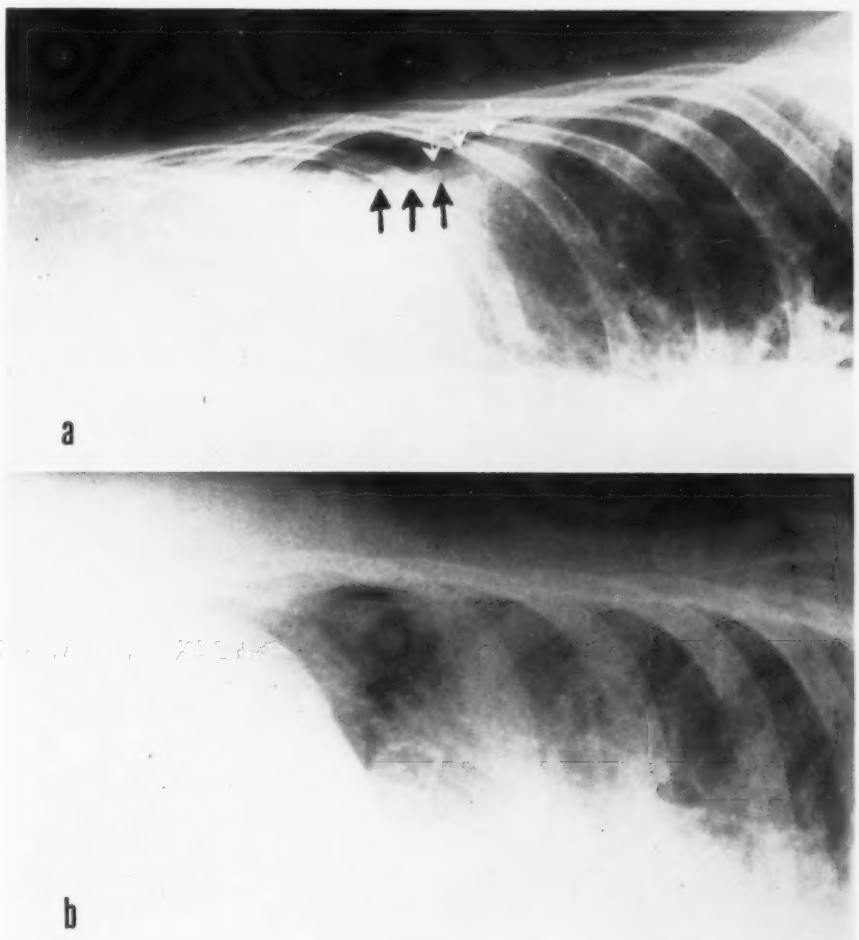

Fig. 4. (*a*) Lateral decubitus view of right chest following removal of 1,500 cc. of fluid and injection of 50 cc. of air into right pleural cavity. *Costophrenic sinus sign* present (pneumothorax not seen on upright films). Fluid level shown by black arrows. White arrows show visceral pleura of partially collapsed lung. Note that the costophrenic sinus is deformed by pleural adhesions. (*b*) Lateral decubitus view of right chest following traumatic thoracentesis and injection of 100 cc. of air into pleural cavity. *Costophrenic sinus sign* absent; pleural adhesions have probably sealed the sinus. Note that the free air is easily detected and that the detached visceral pleural line is seen at right angles to the curve of the ribs.

obtain in patients unable to stand or sit for upright views because the patient lies on the unaffected side. The procedure is also simple in infants.

When the use of roentgen equipment which does not give fine film detail is necessary, the lateral decubitus view is especially useful. The characteristic shape of the costoprenic sinus in pneumothorax is in itself fairly diagnostic. Also, the probability of detecting the detached visceral pleural line is greater in the lower part of the chest than in the apical region.

The view does not replace upright films; it supplements them. A pneumothorax completely confined within pleural adhesions may be overlooked on lateral decubitus films. The extent of the pneumothorax is difficult to judge from lateral decubitus films alone because slight changes in the positioning of the patient, especially in regard to elevation of the lower chest, produce varying shapes to the air-filled costophrenic sinus.

SUMMARY

1. Roentgenographic examination of the chest in the lateral decubitus position has been found useful in detecting the presence of small pneumothoraces when a definite diagnosis could not be made on conventional upright posteroanterior inspiratory and expiratory roentgenograms.

2. The *costophrenic sinus sign* has been explained and illustrated with diagrams and reproductions of roentgenograms.

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VISIBILITY OF PULMONARY STRUCTURE WITH SPECIAL REFERENCE TO EXCISED LUNG

By CHARLES PATCHIN ODERR, M.D.
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BURGER[1] of the Netherlands and Newell and Garneau[2] in this country have studied the visibility of certain phantoms in relationship to the lungs *in situ*. Their findings indicate that the thickness required for a phantom to be visible increases very rapidly when its diameter falls much below half a centimeter. The parenchymal structures of the lung are considerably below this threshold of visibility. This is true even under the most favorable circumstances with regard to the patient and the apparatus. However, if one studies lungs which have been removed from the body, many of the finer structures come within the range of visibility.

Resink[4] has studied excised lungs stereoscopically with a conventional roentgen tube and has shown that almost all of the visible detail represents actual structures and not summated shadows. Summated shadows are, for the most part, background density or densities not in any way resembling the individual structures. On the other hand, the amount of *detail* which is visible is dependent on other factors which were not studied. His photographs, as well as those of Greening and Pendergrass,[2] demonstrate the limitations of the conventional roentgen tube for visualization of pulmonary detail due to its relatively large focal spot and relatively great inherent filtration.

The 0.3 mm. focal spot roentgen tube improves the visibility with regard to size, but the inherent filtration of the standard fractional focal spot tube still blocks the very soft rays which are needed to produce roentgenographic shadows of the delicate pulmonary parenchyma. The parenchymal structures are not only small and thin, but are also of light density. As a result of these considerations, we shifted to a beryllium window tube for study of excised lung. With this we saw, for the first time, a recognizable representation of pulmonary parenchymal detail. Single alveoli are not shown, but patterns composed of multiple layers of alveoli and small vessels are demonstrated. Vessels as small as 0.01 mm. in diameter are visible. By cutting thinner and thinner slices of the lung,* one obtains progressively clearer representations of the unit structures. However, the thinnest slice that the beryllium window† radiation would record on available film was still thick enough to contain many layers of primary lobules.

For the slices below 1.0 mm. thickness,‡ the best film representation of parenchymal structure was obtained by what we have termed a fluorescent photograph. To produce this the specimen is sandwiched between a slow intensifying screen and a type M industrial film. The "sandwich" is placed in a tight-fitting cassette and exposed to approximately 20 ma. sec. at 120 kv. peak and 36 inch distance. The small amount of of roentgen ray that reaches the film produces a minimal, or possibly negligible effect on the slow emulsion. The principal factor effecting the emulsion is the fluorescent light. By this method individual alveolar walls and individual alveolar spaces can be identified when the film is examined with a lens, or enlarged photographically. Ten times magnification is a comfortable degree of enlargement.

The anatomic study can be extended by sectioning in different planes. Sagittal, coronal, and cross section planes have been used. Sections of varying thicknesses are cut and each thickness used according to the method best adapted to it; *i.e.*, beryl-

* It was possible to do this after the lung was dried out in the inflated condition.

† Beryllium window on the unit used was 0.08 inch thick.

‡ Optimal thickness is 0.1 to 0.3 mm.

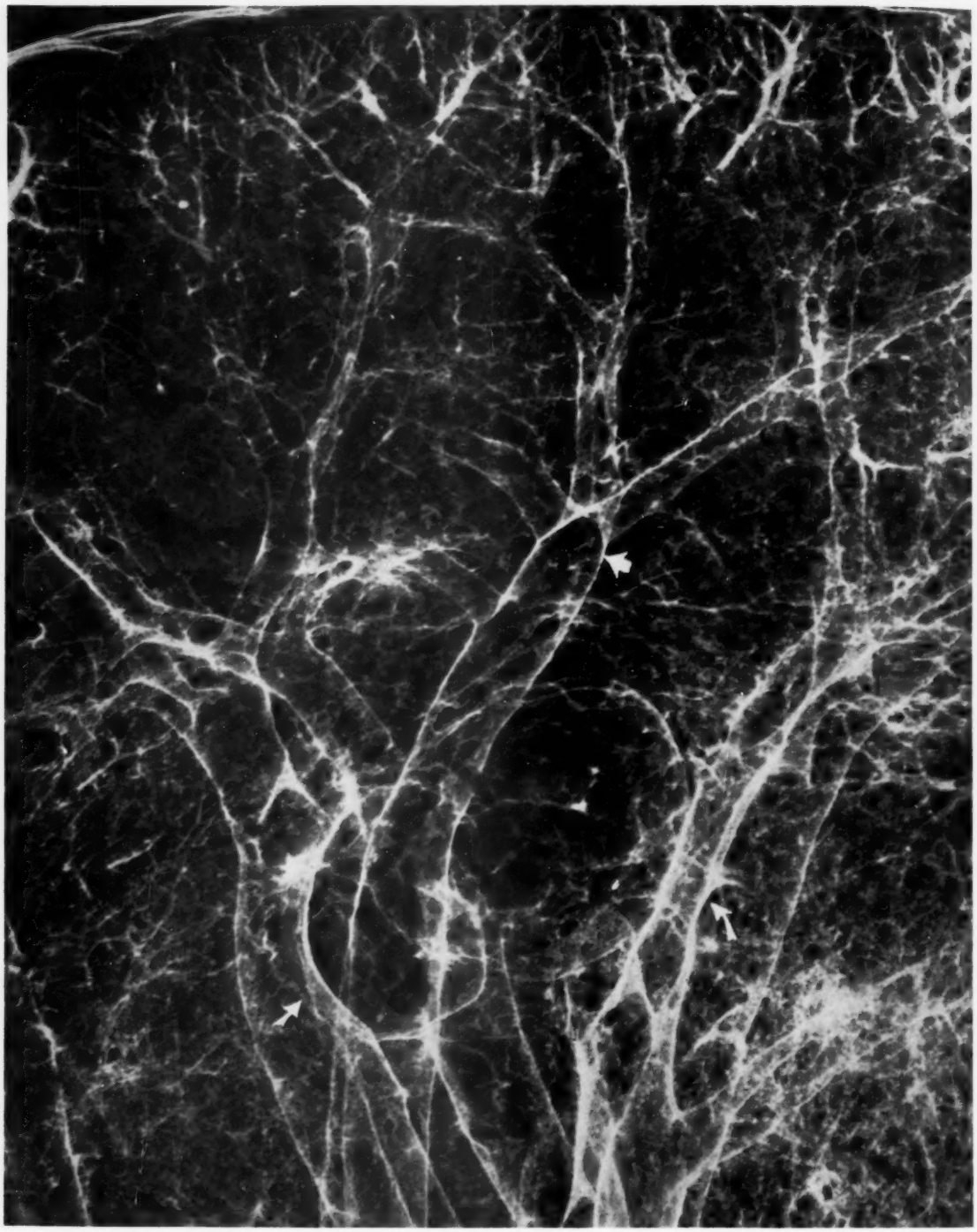

FIG. 1. Beryllium window roentgenogram (20 kv. peak) of a cross section of dried normal lung. Note bronchial artery (slender straight arrow) on the left hand bronchus, and small cyst connection to right hand bronchus (curved arrow). Each of these bronchi have their associated pulmonary artery showing. A pulmonary vein (thick straight arrow) is between, and is larger. Section is ±1 cm. thick. From an enlargement ×6.

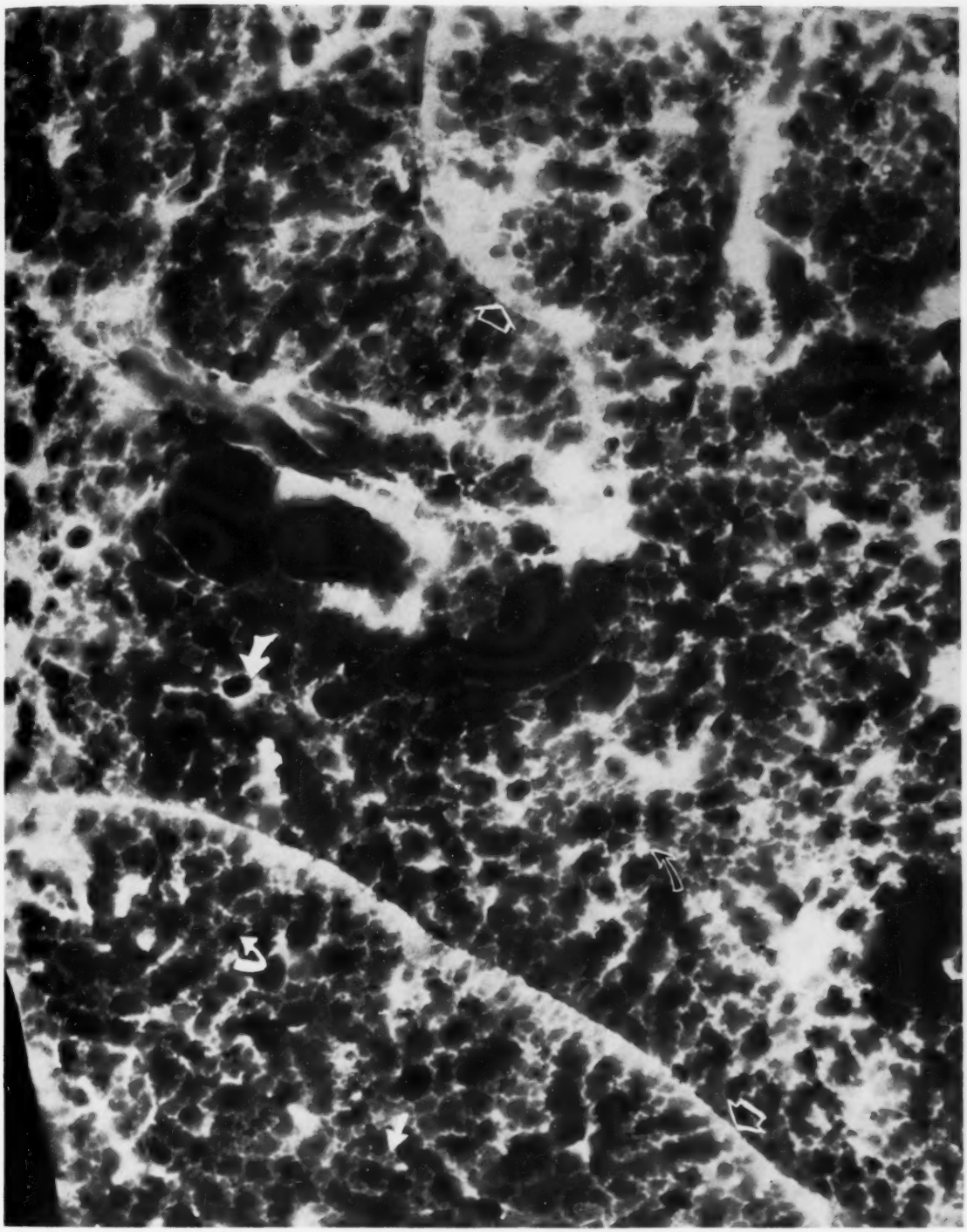

Fig. 2. Fluorescent photograph of dried normal lung from a man aged seventy. Note how the smallest units, representing alveoli (slender solid arrow), cluster about larger units, representing sacculi ("U-turn" arrow). The sacculi with adjoining atria and ducts seem to occupy the major portion of the total volume. Bronchioles of various sizes and accompanying pulmonary arteries are identifiable (thick straight arrow points between one such pair). Pulmonary veins (slender outlined arrow) are seen without accompanying bronchus. Delicate septa (thick outlined arrows) dividing the lung into secondary lobules are clearly shown, and lymphatic channels accompanying septa are faintly visible. Section is ±0.1 mm. thick. From an enlargement ×6.

lium window roentgenography for sections above one millimeter and fluorescent photography for sections below one millimeter. In the thicker sections one can study the systems of branching of the vessels and bronchi. From such a study one gets the impression that, embryologically, the *shapes* of the lobes must be set first because the pattern of vascular and bronchial supply seems to be determined by the adoption of the optimum branching system for each space requirement. The visibility of the pattern formed by multiple layers of terminal bronchioles is not as good as that of the smaller vascular terminations. The reason for this is the lack of strong contrast such as is provided for in the small vessels by dried blood. The *dried* blood in the small vessels makes them traceable roentgenographically in sections several centimeters thick. *Medium* sized vessels which have been drained of blood and distended with air are remarkably similar roentgenographically to the air-filled bronchi, and the two may be difficult to differentiate. One can identify the larger vessels by tracing them out to a zone where their lumina contain dried blood. The further distinction between arteries and veins is made by position. The arteries accompany the bronchi, and the veins course through the parenchyma alone. The veins occupy positions between the arteriole-bronchiole sets, somewhat analogous to the anatomy of the hepatic veins. The hepatic veins are solitary in contrast to the hepatic arteries, which are accompanied by biliary ducts. Bronchial arteries have also been seen and

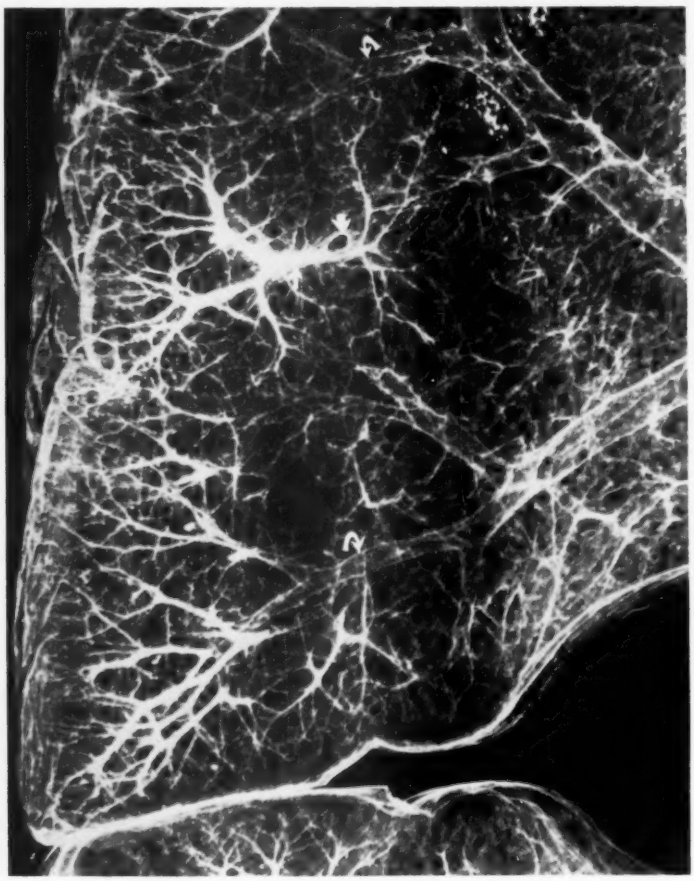

FIG. 3. Beryllium window roentgenogram of normal lung showing good filling of small vessels with dried blood. Pulmonary vein ("U-turn" arrow). Pulmonary artery (slender straight arrow). Bronchus (thick straight arrow). Section ±0.5 cm. thick. From an enlargement ×5.

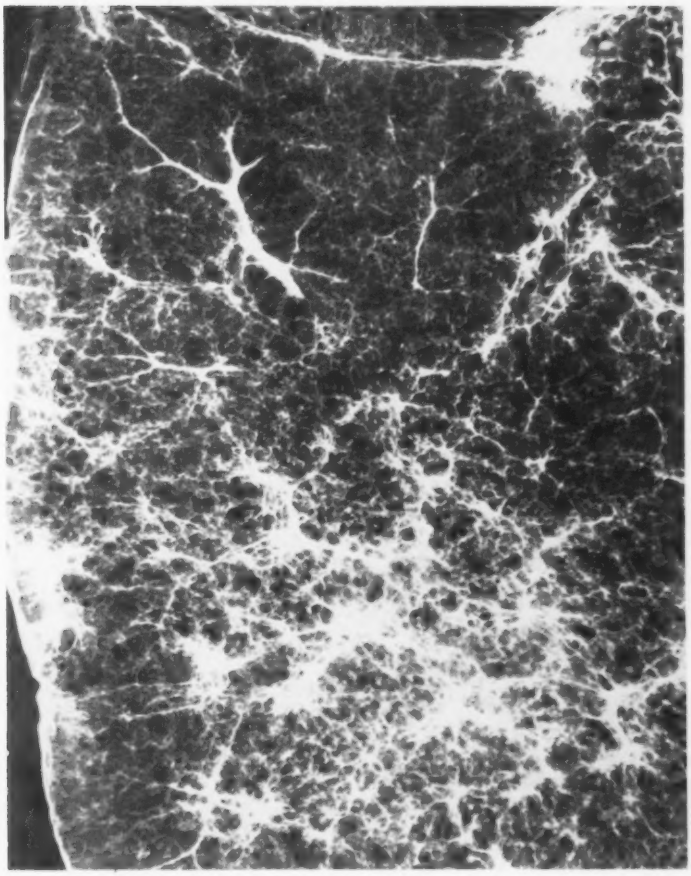

Fig. 4. Beryllium window roentgenogram of lung from a patient with collagen disease (lupus erythematosus). Note destruction of normal architecture and loss of vascularity due to fibrosis. Section ±1 cm. thick. From an enlargement of ×5.

their terminations near the level of respiratory bronchioles demonstrated.

The terminal ramifications of the bronchioles are *traceable*, by fluorescent photography, into alveolar sacs and into individual alveoli. This depends, of course, on finding areas where the related terminal structures happen to course in the plane of the thin slice.* The smallest air spaces visible (alveoli) in fluorescent photographs are close to 0.1 mm. in diameter and the walls of these structures are perhaps a tenth of the diameter of the lumen, or about 0.01 mm. (10μ). Many alveoli were larger. We were suprised and gratified at the degree of sharpness produced in the fluorescent photograph of these parenchymal structures.

The measurements of the sacculi, atria, ducti, and respiratory bronchiole in a man of seventy varied from 0.2 mm. to 0.8 mm. but seemed to be widely variable in different parts of the lung.†

The delicate septa, which to some degree divided the lung into secondary lobules, were clearly visualized in the fluorescent photographs. The evidence that these structures divide the pulmonary segments into completely separate units is lacking, but they do appear to form at least an incomplete three dimensional mosaic pattern,

* It is expected that the continuity of the terminal air-containing structures will be best demonstrated by a thinner beryllium window than was available for this study.

† Dried specimens will naturally show increased diameter of lumina and corresponding shrinkage of wall thickness. The ratio between the thickness of a dried wall and its thickness in the "wet" state has not been determined.

with units intermediate in size between that of the primary lobule and the bronchopulmonary segment.

Smaller lymphatic vessels around blood vessels and bronchi are visible when seen in cross section. The larger lymphatic vessels associated with pleural surfaces are identified by their location and their valves. These course through many secondary septa as well as through the major fissures.

Under the binocular dissecting microscope, the three dimensional mosaic pattern formed by the air sacs of the primary lobules is remarkably well demonstrated. By using various combinations of reflected and transmitted light and changing the focal plane as one studies a given field, it is possible to follow the details of the structure through layers several hundred times as thick as ordinary sections. Capillaries of 0.01 mm. in diameter are visualized throughout most of their length. Elastic fibers, septal (epithelial) cells, lymphocytic aggregations, as well as capillary networks in the bronchial walls, are all visible.

CONCLUSION

Beryllium window roentgenography and fluorescent photography are useful methods for studying the anatomy and pathology of excised lung when the specimen can be dried in the inflated state. Structures far below the visibility threshold for either clinical or postmortem roentgenograms, made with conventional tubes, are clearly shown. Beryllium window roentgenography demonstrates vessels as small as 0.01 mm. in diameter, and visualizes patterns produced by alveolar walls. Fluorescent photography visualizes individual alveoli.

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TESTING OF PHOTOFLUOROGRAM INTERPRETERS BY THE USE OF PHANTOMS WHICH PRODUCE FALSE INFILTRATES SIMILAR TO TUBERCULOUS LUNG LESIONS

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WHENEVER the reliability of a roentgenographic method used in a lung survey has to be tested, it is essential to achieve, or to possess, precise information about the lung status of the subjects composing the study group. This knowledge can only be obtained if both a reliable roentgenographic method and a procedure of interpretation which gives accurate readings are present.

The first attempts to analyze these problems and to fulfill the above conditions were done by American teams, each consisting of radiologists, chest specialists and a statistician. Their work resulted in a series of papers.[1,5,6]

These attempts disclosed the subjective errors in independent interpretations of roentgenograms and photofluorograms of the lungs, *i.e.*, the inability of a reader always to agree with other readers, or to be consistent with himself in his interpretations of the same set of films. This interindividual variation and intraindividual inconsistency in the interpretation was not small and constituted a major obstacle in the attempts of the investigators to reach unanimous and, thereby, unambiguous interpretations during the studies mentioned above.

Thus, in the testing of roentgenographic methods,[1] it was impossible to define the lung status of the subjects composing the study group. When photofluorographic interpretations were tested,[6] it was difficult to decide with certainty which photofluorograms contained lesions which should have been noticed by the interpreters. Here the use of roentgenograms as "umpires" did not help because both the independent readings and the group readings of the roentgenograms taken during the ensuing follow-up examination were influenced by the inevitable interindividual variation. An increase in the number of readings will diminish this uncertainty in the interpretation of each of the roentgenograms, but will also increase the number of "questionable" roentgenograms, *i.e.*, those roentgenograms where a unanimous interpretation cannot be achieved and which have to be omitted if only absolutely accurate interpretations are acknowledged.

Some of the above inconveniences may be avoided if a suitable number of photofluorograms in a study contains artificial lesions (false infiltrates) similar in size, texture and contrast to small tuberculous lesions in the lungs.

This is achieved by the use of phantoms. Follow-up examination with an "umpire-method" is then unnecessary and the identification and the correct interpretation of the "abnormal" photofluorograms will present no problem. Before such phantoms are made, patients known to have small tuberculous infiltrates in the lungs are roentgenographed on full-sized films. By means of visual comparison and densitometry, the phantoms are adjusted to produce similar shadows (false infiltrates) when they are roentgenographed through a human chest on full-sized films. Figure 1 shows a roentgenogram with a false infiltrate in the left second intercostal space produced by phantom no. 5 on a full-sized film.

For the present study a series of phantoms was made which produced false infiltrates on full-sized films roughly from

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Fig. 1. Roentgenogram of phantom no. 5. The false infiltrate in the left second intercostal space is produced by roentgenographing the phantom through a normal chest on a full-sized film.

8–10 mm. by 11–12 mm. up to 16–17 mm. by 18–19 mm. in size. These figures are uncertain because it was impossible to give the precise borderline between the false infiltrates and the normal lung tissue. It was still more difficult to measure the densities of the false infiltrates and of the surrounding lung fields, attempting to give figures of contrast. However, when the false infiltrates were superimposed on lung tissue, or on a rib as well, the contrasts ranged from about 0.1 to about 0.4.

Photofluorograms containing false infiltrates are made by exposing the phantoms through the chest of persons known to have normal lungs. Figure 2 shows a 70 mm. photofluorogram containing a false infiltrate situated in the left first intercostal space and behind the second rib, *i.e.*, in the middle of square H-3 in the system of reference. The false infiltrate is produced by the above mentioned phantom no. 5.

It needs to be pointed out, however, that because the phantoms are outside the chest and near the fluorescent screen, there will be no unsharpness caused by movements or by the size of the anode. These objections are perhaps not vaild because the two factors have already influenced the lung lesions which are imitated. When photofluorographed, a "natural" lung infiltrate is always additionally enlarged because the anode-screen distance used in photofluorography is shorter than the anode-film distance used in roentgenography.

False infiltrates, however, are not similarly enlarged in the photofluorogram because the phantoms are placed near the fluorescent screen and the cassette, and thereby are not influenced by a change in distance. Thus, the interpreters are able to discover false infiltrates which correspond to smaller ones than those created in the roentgenograms, aided perhaps by the ensuing steeper opacity gradient of the false infiltrate in the photofluorogram.

To ensure an accurate localization of the false infiltrate in the photofluorogram, the

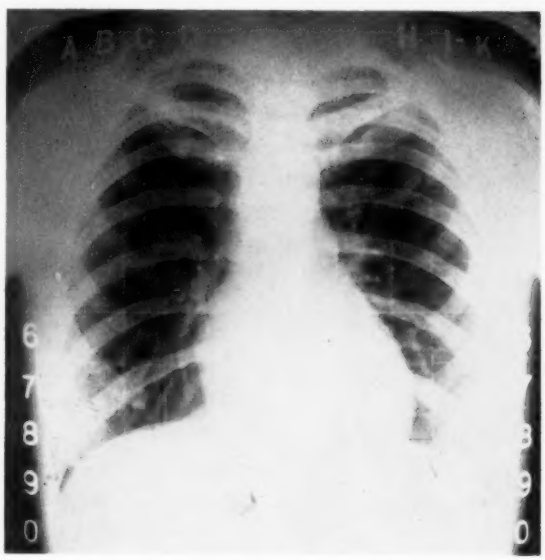

Fig. 2. A 70 mm. photofluorogram with a false infiltrate situated in the left first intercostal space and behind the second rib, *i.e.*, in the middle of square H-3 in the system of reference. The false infiltrate is produced by roentgenographing phantom no. 5 through a normal chest.

chest and the phantom are exposed through a graph of reference which causes a roentgenographic shadow.[2,3] The graph of reference is inside the board to which the phantom is attached and corresponds to a system of reference painted on that side of the board which faces the fluorescent screen during the exposure. In this way, it is possible to know exactly in which square the false infiltrates will appear in the photofluorogram. Figure 3 shows a 70 mm. photofluorogram of the graph reference and of phantom no. 5 situated in square H-3. Figure 4 shows the board mounted, by means of hinges, on the front plate of a 70 mm. photofluorograph. In square H-3, phantom no. 5 is attached to that side of the board which faces the front plate during the exposure.

In *Uppsala, Sweden*, I have had the opportunity of making a test-film comprised of 53 mm. by 53 mm. photofluorograms. The above mentioned board with the graph of reference was placed over the fluorescent screen and 101 persons were photofluorographed. One phantom was attached to the board 38 times and 2 phantoms 20 times, and the identification numbers of the squares in the graph of reference and of the phantoms noted. It had to be determined on which photofluorograms the relevant squares were situated inside the visible parts of the lung fields. Only these films were to be identified as 'positives' by 10 readers in an investigation of the efficiency of interpreters conducted at the Mass Radiography Centre of the Royal Swedish Medical Board in Stockholm. Some results of the experiment are shown in the tables accompanying this article.

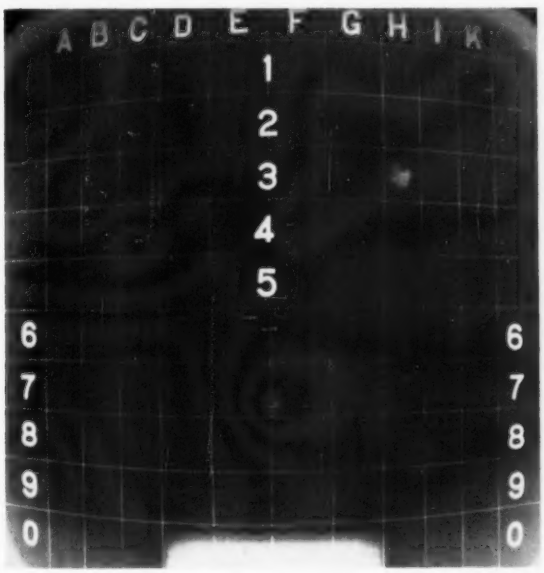

Fig. 3. A 70 mm. photofluorogram of the board to which phantom no. 5 is attached, showing the roentgen shadow of the phantom and of the graph of reference. When the photofluorogram shown in Figure 2 was made, the whole system was roentgenographed through a normal chest.

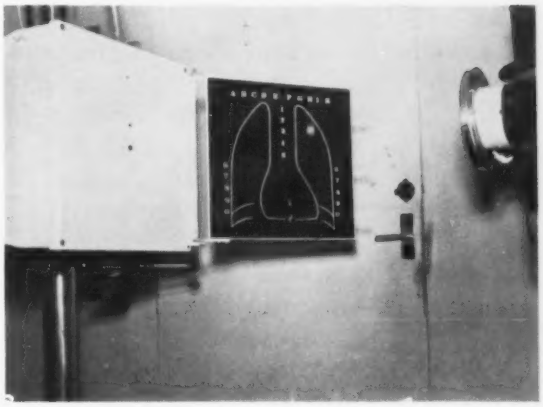

Fig. 4. The board is mounted by means of hinges attached to the front plate of a 70 mm. photofluorograph. The board contains a graph of reference which produces a roentgen shadow. A system of reference in congruity with this graph is painted on that side of the board which faces the front plate when the board, during the exposure, covers the fluorescent screen. Phantom no. 5 is attached to the board in the square H-3.

During the readings the individual routine of the readers was not interfered with; however, the noting of the squares in which the false infiltrates were found had to be added as a supplement to the usual anatomic localization. The nature of the lesions was not revealed, thereby causing no embarrassment to the readers when describing the texture of the lesions or when recommending follow-up examination.

The study only concerned identification of false infiltrates, and the correctness of a reading was based upon the localizing of the false infiltrates in the correct squares in the

graph of reference and not on the decision of a follow-up examination. A misinterpretation, if such can be said of false infiltrates, did not influence the score of an interpreter.

Under these conditions 59 of the false infiltrates were noticed by one or more of the readers. Based on these readings alone, it is not possible to decide whether any of the remaining false infiltrates were identifiable at all.

Table 1 shows for each of the 10 participating interpreters the number of false infiltrates noted and the corresponding percentage based on the combined score of 59 identifications. The table also gives the cumulative number of identifications gained during multiple readings when the efficiency through each reader added was (1) increasing and (2) decreasing.

Table 1 shows such great variation in the results of the readings by the 10 interpreters that the score is doubled from the least to the most successful reader. This must be taken into account when partners for dual readings are selected. Supposed dual readings by teams of either less successful or more successful readers gave a calculated average score of 42.7 identifications of false infiltrates; but if the readers of the above 2 categories were interchanged, the average score was 46.5 identifications. That means a 10 per cent increase in the efficiency, without a corresponding increase of the work involved.

TABLE I

FALSE INFILTRATES IDENTIFIED

Readers' Code-Number	Number	Per Cent of 59	Cumulative Number (1)	Cumulative Number (2)
1	24	41	24	59
2	26	44	31	59
3	31	53	34	59
4	34	58	43	59
5	39	64	47	59
6	39	64	52	58
7	39	64	57	57
8	43	73	57	56
9	46	78	59	56
0	48	81	59	48
Average	37	63		
Identified by at least one reader	59	100		

The table shows for each 10 readers the number of false infiltrates noted and the corresponding percentage based on a combined score of 59 identifications. Also is given the cumulative number of identifications gained during multiple readings when the efficiency through each added reader was (1) increasing and (2) decreasing.

Due to the difference in efficiency, the number of independent readings necessary to ensure identification of a maximum number of false infiltrates is influenced by the position of the more successful readers in the sequence of readings. Many different sequences are possible but only 2 are mentioned: the one with an ever increasing and the one with an ever decreasing efficiency attributable to each reader added (1 and 2 in Table 1). In the first sequence the maximum number of identifications is reached after 9 independent readings and in the second after 6 readings, one of the readers not increasing the yield. In the present study it is impossible to reach the maximum number of identifications until those 4 readers who have made unshared identifications have participated. Therefore, the optimal sequence probably consists of about 5 of the most successful readers.

In a study on the efficiency of interpreters, the number of identical interpretations considered necessary to ensure the correctness of a statement, positive or negative, is in fact a matter of choice. In order to ascertain how this choice might affect the results gained, an investigation as to how the efficiency of each of the 10 readers in the present experiment was influenced by a presumed variation in that number of identical interpretations was made.

Table II shows how often a false infiltrate had been identified by a varying number of readers and how often each of the 10 readers participated in these identifications.

TABLE II

NUMBER OF TIMES EACH OF THE FALSE INFILTRATES WAS IDENTIFIED BY A VARYING NUMBER OF READERS AND HOW OFTEN EACH OF 10 READERS PARTICIPATED IN THESE IDENTIFICATIONS

Number of Readers in Agreement	Number of False Infiltrates Identified	Number of Times Each of 10 Readers Participated in the Identifications										
		1	2	3	4	5	6	7	8	9	0	Average
all readers	15	15	15	15	15	15	15	15	15	15	15	15
at least 6 readers	31	22	25	30	25	30	27	30	31	29	31	28
at least 4 readers	42	24	26	30	31	36	33	34	41	37	39	33
at least 1 reader	59	24	26	31	34	39	39	39	43	46	48	37

The table therefore gives the number of false infiltrates accepted to be present under the corresponding definitions of an accurate interpretation, and the number of accurate interpretations of each of the 10 readers.

As mentioned above, 59 false infiltrates were noticed by at least 1 of the interpreters. If one identification is assumed to be enough to confirm the presence of a false infiltrate, the average score is 37, or 63 per cent and the difference in scores between the least and the most successful reader is 100 per cent. If at least 4 correct identifications are considered necessary, the average score is diminished by 4, to 33; nevertheless, the average score in percentage increases to 80, since the total number of false infiltrates accepted has decreased to 42. This difference of 17 had been built up by contributions from 8 of the readers. The difference between the 2 readers mentioned above is now only 70 per cent. If 6 or more correct identifications are considered necessary, the average score is further reduced to 28, but the average score in percentage increases to 90, being 100 for 2 of the interpreters, since the total number of false infiltrates accepted has decreased to 31. The difference in efficiency is now only 40 per cent.

Thus, the analysis shows that in the present study efficiency figures were influenced by the conditions considered necessary to ensure the accuracy of an identification. The apparent efficiency increased whenever the conditions were more exacting with the result that at the same time the interpreters in ever increasing degree appeared more equal and better matched.

It is evident that the cumulative increase in the number of identifications influences the apparent efficiency of each of the readers in the study. The greater the number of readers, the greater will be the number of false infiltrates identified by at least 1 of them, until the maximum number of false infiltrates have been identified. Correspondingly, the over-all efficiency of the entire group of participating readers will be constantly decreasing.

In an effort to investigate whether the apparent efficiency of an interpreter is influenced by the efficiency of the other readers participating in a study, the 10 readers were divided into 3 groups. The readers in Group I had an average efficiency of 46, in Group II of 64 and in Group III of 77, all in percentage of a total score of 59 identifications. Each of the readers in the 3 groups was then presumed to have made dual readings with members of his own and the 2 other groups. The apparent efficiency of each of the 3 groups was then calculated as the average of the individual scores achieved by each reader in the group during these supposed dual readings. Table III gives the average apparent efficiency achieved by the readers in each of the 3

TABLE III

THE AVERAGE EFFICIENCY (IN PERCENTAGE) OF 3 GROUPS OF READERS WHEN ASSESSED BY MEANS OF SUPPOSED DUAL READINGS WITH READERS FROM OWN GROUP AND WITH THE 2 OTHER GROUPS

	Partner in the Supposed Dual Reading from Group		
	I	II	III
Group I	85	66	58
Group II	95	81	78
Group III	98	91	86

groups during supposed dual readings with their own group and with the 2 other groups. The table shows that the efficiency is nearly the same in all 3 groups when members of the same group act as partners. However, if the partners are from 2 different groups, the apparent efficiency decreases for the readers in the lower group and increases for readers in the higher group.

The results of the readings by the 10 interpreters indicate that the apparent efficiency of readers in a study, when based on the total score gained by the readers during independent readings, is affected by factors already decided upon during the planning of the study. Two of the factors, the definition of a positive photofluorogram and the number of participating interpreters, can be influenced directly. Thus, it is possible to prejudice the apparent efficiency of the participating readers. The more exacting the conditions for a verdict of positiveness and the smaller the number of readers chosen, the higher the apparent efficiency of the participating readers. Moreover, they will appear well matched and equals. A third factor, the relative and absolute skill of the interpreters is *a priori* unknown and therefore cannot be taken into account during the planning, unless those "experienced" and "less experienced" are chosen as partners in a study. Such a matching will greatly enhance the efficiency of the experienced readers and decrease the efficiency of the less experienced readers.

SUMMARY

The interindividual variation and the intraindividual inconsistency of interpreters during independent readings of photofluorograms of the lungs constitute major difficulties in the evaluation of the accuracy of photofluorographic interpretations.

These inherent subjective errors pose the dilemma of choosing between a high probability and a comprehensive accuracy in the interpretation.

The solution of this dilemma has been aided somewhat by a study with phantoms producing false infiltrates which are similar to natural lung lesions in size, texture and contrast. A test-film consisting of 101 53 mm. by 53 mm. photofluorograms has been made and read independently by 10 interpreters. Because of the quality of the film, an identification made by one single reader sufficed to ensure the correctness of an interpretation and to prove the perceptibility of a false infiltrate.

Fifty-nine of the false infiltrates were noticed by at least one of the readers and the average score of the 10 readers was 37, or 63 per cent, with a variation of from 24 to 48 identifications.

Based on these results it can be stated that the number of identical readings considered as necessary to prove the presence of a false infiltrate (and thereby the accuracy of a reader's interpretation) influences the efficiency of the readers in the percentage of the total number of identifications under the different conditions. The greater the number of the required readings and the more exacting the conditions, the higher the efficiency of each individual reader, and likewise the higher the number of equally matched interpreters.

The efficiency of interpretation is also influenced by the number of readers participating as a team, and by the relative skill of the readers. The lower the number,

the higher will be the efficiency credited to each individual reader; the greater the difference in skill, the higher will be the efficiency of the relatively more successful readers.

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***Thirty-ninth** Annual Meeting:* Chateau Frontenac, Quebec City, Canada, May 29–June 1, 1957.

EDITORIALS

CLINICAL RADIOLOGY AND STUDIES OF PULMONARY FUNCTION

PRECISE information concerning the function of the lungs can be obtained by physiologists using fundamental knowledge which has come from painstaking research over the last twenty years. The delicate interaction between mechanical factors of breathing and gas exchange, and the biologic factors facilitating or impeding this basic function, can be analyzed step by step. Mathematical formulas and logarithmic graphs condense much of this information for easy reference. Investigations of pulmonary function have been so searching and the knowledge compiled so detailed that the situation is analogous to that relating to kidney function or cardiac hemodynamics. How is the practicing radiologist to approach this body of knowledge and make use of it in clinical problems pertaining to the chest?

Basic knowledge concerning pulmonary function[2] is available to the radiologist and should be considered first. Preliminary attempts to relate some of this knowledge to clinical radiology[1] should be the next step. Beyond this point, the inquiring mind and intellectual capacity of the radiologist in clinical practice can chart his course. We are continually challenged to apply results of physiologic investigations to medical practice.

For example, although lung volumes are relatively easy to measure, they vary so widely in healthy persons that figures obtained for pulmonary capacity do not necessarily reflect the presence of pulmonary insufficiency. The most important aspect of pulmonary ventilation is the *amount* of air that reaches the *alveoli* and the *uniformity* with which it is distributed to them. To obtain this information requires specialized laboratory procedures and interpretation of results by a trained physiologist.

However, experience gained by testing can be used in clinical evaluation even when special testing methods are not available. Any condition where air is prevented from reaching alveoli in sufficient amounts results in hypoventilation with its consequences, anoxemia, CO_2 retention, and respiratory acidosis. Diseases leading to airway obstruction (asthma), mechanical inadequacy in respiratory movements of the chest (poliomyelitis) and irregular distribution of air to alveoli (emphysema) produce hypoventilation.

Even with optimum alveolar ventilation, anoxemia may be present if alveolar capillary blood flow is not regular and uniform, and the efficiency of matching of alveolar ventilation and alveolar blood flow can be determined by appropriate laboratory procedures.

Variations in alveolar ventilation/blood flow ratios may be diagnosed by exclusion in anoxemic patients. Hypoventilation can be eliminated by simple clinical tests (lung capacity, roentgenograms for anatomic changes). Impaired diffusion of O_2 across the alveolar capillary membrane can be measured by more elaborate physiologic tests (CO uptake). If these conditions are excluded, the presence of an anatomic shunt allowing mixture of venous and arterial blood can be determined by giving

[1] Barden, R. P., and Comroe, J. H., Jr. Roentgenologic evaluation of pulmonary function: Correlation with physiologic studies of ventilation. Am. J. Roentgenol, Rad. Therapy & Nuclear Med., 1956, 75, 668–681.

[2] Comroe, J. H., Jr., Forster, R. E., DuBois, A. B., Briscoe, W. A., and Carlsen, E. The Lung: Clinical Physiology and Pulmonary Function Test. Year Book Publishers Inc., Chicago, 1955.

the patient O_2 to breathe instead of air. If a shunt exists arterial saturation will never reach the normal value of 100 per cent.

Differential diagnosis of this type can be of great importance since hypoventilation, anatomic shunt, and reversible airway obstruction, all leading to anoxemia, require very different methods of treatment.

Structural changes in the alveolar walls may produce anoxemia in the presence of normal alveolar ventilation and alveolar blood flow by imposing a barrier to the passage of O_2 across the alveolar-capillary membranes. This occurs in patients with pulmonary fibrosis (sarcoidosis or silicosis), pulmonary emphysema, advanced mitral stenosis, and after pneumonectomy. It can be detected clinically, by determining that arterial O_2 saturation falls *during exercise* and is restored to normal values during the inhalation of O_2.

Many clinical examples which demonstrate the practical application of physiologic testing to interpretation of disease are discussed by Comroe, *et al.*[2] The following illustration is quoted from this source, "The patient is a 68-year-old cigar maker who has had several attacks of fever with cough and sputum (some-times blood tinged) in the past six months. Shortly before study, dyspnea and palpitation developed on exertion and were becoming progressively more severe."

"He has a large chest. The percussion notes are hyperresonant and breath sounds distant. There are no rales. Radiological study shows marked pulmonary emphysema with no evidence of localized disease; fluoroscopic examination reveals that the pulmonary artery branches are larger and more pulsatile than normal. Clinical diagnosis: emphysema. The pulmonary function tests were performed as a routine study." (Values for lung volumes, ventilation, and mechanics of breathing are then given, and all are normal. Only anoxemia of arterial blood is found which becomes normally saturated when the patient is given O_2 to breathe.) To continue: "Despite the clinical and radiological impressions, the physiologic tests make the diagnosis of emphysema untenable because (1) distribution of inspired gas is normal and (2) the MBC and maximal expiratory flow rate are normal. The anoxemia cannot be due to hypoventilation, since alveolar ventilation is normal, or to uneven distribution of gas, since distribution is uniform. The anoxemia cannot be attributed to a shunt, because the arterial blood (hemoglobin and plasma) became maximally saturated with O_2 when the patient breathed 100% O_2. The low arterial O_2 saturation must, by exclusion, be due to *impairment of diffusion* across the alveolar capillary membranes or to *uneven distribution of pulmonary capillary blood flow*. (At the time this patient was studied, tests of diffusing capacity were not available.)"

"The patient died six weeks later, and autopsy revealed multiple pulmonary emboli, but none of the classic signs of emphysema. The physiological disturbance must, then, have been due to uneven pulmonary capillary blood flow without uneven distribution of inspired gas."

"Study of this patient emphasizes (1) that the clinical and radiological diagnosis of emphysema is frequently in error, (2) that pulmonary embolism need not lead to typical radiological changes, (3) that pulmonary embolism need not interfere with pulmonary ventilation or with the uniformity of distribution of inspired gas, and (4) that disorders of the alveolar-capillary membranes or of the pulmonary circulation can be diagnosed in some cases without specific tests, by a process of exclusion."

Shapiro and Rigler[3] and Westermark[4] have noted the occasional difficulty in distinguishing avascular pulmonary infarcts from areas of localized emphysema in roentgenograms. When more radiologists become interested in abnormal pulmonary physiology, greater diagnostic service may be

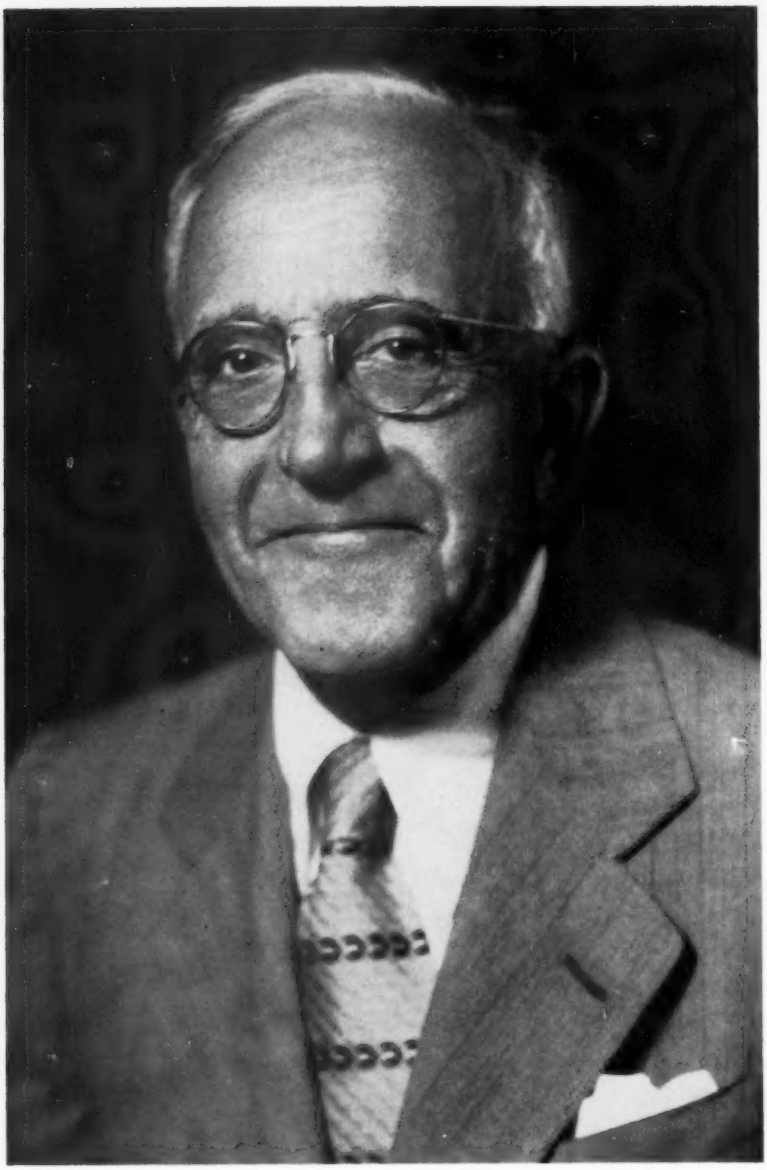
[3] SHAPIRO, R., and RIGLER, L. G. Pulmonary embolism without infarction. AM. J. ROENTGENOL. & RAD. THERAPY, 1948, *60*, 460–465.

[4] WESTERMARK, N. Roentgen Studies of the Lungs and Heart. University of Minnesota Press, Minneapolis, 1948.

given patients with obscure diagnoses, such as in the case quoted above.

Radiologic examinations of the chest should include attempts to obtain qualitative estimations of pulmonary function. The radiologist fortunate enough to have his patients studied in a pulmonary function laboratory will become fascinated by the results of correlating radiologic information with that obtained by physiologic testing. These few favored radiologists can help the many of us develop potential information not acquired in chest examinations done by routine methods alone. It is up to the many of us to know enough to demand more help from every source in order to extend our physiologic point of view.

Robert P. Barden, M.D.



THEODORE WEST
1885-1957

DR. THEODORE WEST died on January 4, 1957, after a short illness. He was born in Springfield, Illinois, on August 31, 1885, and received his preliminary education in Lincoln, Illinois. After his graduation from Albany Medical College in 1916, he interned at Albany Hospital.

Dr. West served in both World Wars and had a distinguished and somewhat unique military career. He entered the Army Medical Corps in 1917 as a Lieu-

tenant and rose to the rank of Captain before his discharge in 1919. In World War II he returned to the Army in 1941, and terminated his service with the rank of Lieutenant-Colonel in 1945.

All of Dr. West's professional life was devoted to the practice of roentgenology. In 1919, he became head of the Department of Roentgenology at the United Hospital, Port Chester, New York, from which post he retired in October, 1956. After almost thirty-eight years of distinguished practice at that institution, he was honored by being designated Director Emeritus.

Dr. West followed in the paths of his forebears. His maternal grandfather, Dr. John Allen, served in the Civil War as a contract surgeon, while his paternal grandfather, William D. West, was a Captain, Engineers, in the Mexican War. His father, William D. West, was a Private in the Civil War. Dr. Harold C. West, his brother, practices in Yonkers, New York.

Notwithstanding his busy practice, Dr. West devoted considerable time to his County Medical Society, the Radiological Society of Westchester County, and other professional organizations. After holding several offices in the Westchester County Medical Society, he became president of this organization in 1936. He was Chairman of the Ninth District Branch in 1937. In 1953, Dr. West was elected Chairman of the Westchester Radiological Society. Other societies in which he was active were the American Roentgen Ray Society and the New York Roentgen Society. He became a Diplomate of the American Board of Radiology in 1934 and, subsequently, a Fellow of the American College of Radiology in 1941.

An active Thirty-third Degree Mason, Dr. West was also a past commander of American Legion Post 93 in Port Chester. He attended St. Peter's Episcopal Church.

Dr. West is survived by his wife, Dorothea Arndt West, to whom he had been happily married for nearly forty years.

The goal most men hope for, Theodore West attained. Much prestige and respect had been accorded him. As a truly great physician, he served his patients and his brother practitioners well. To those who came in daily contact with him, his friendship was a grand experience. Certainly his passing leaves a void that will be difficult to fill.

Those of us who were Dr. West's friends salute his memory with the simple words, "Well done."

Arnold M. Wald, M.D.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Die Bronchographie. Von Doz. Dr. F. Stutz, Freiburg/Br., und Doz. Dr. H. Vieten, Düsseldorf. Cloth. Price, DM 66.-. Pp. 250, with 181 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1955.

Those interested in the subject of bronchography will find much of interest in this monograph. For early outstanding work on bronchography, the authors give credit to Jackson as the first to use contrast media in the tracheobronchial system in 1918, and to Lynah and Stewart, in 1921. Bianco, in 1917, had already used some lipiodol, and of course much credit is due Forestier, Leroux and Sicard for their work with lipiodol. Piaggio Blanco and Garcia Capurro, in 1935, and di Rienzo, in 1949, are among others who receive well-deserved mention.

This work, which constitutes a complete manual of bronchography, discusses contrast media, tracheobronchial anesthesia, the technique of application, and the technique of obtaining spot-films or "aimed" bronchograms produced under fluoroscopic guidance. Endotracheal narcosis is also considered, as well as tracheobronchial function. The rest of the book describes the anatomy of the bronchial system, normal and pathologic physiology, and the morphologic changes. Finally, there is a full consideration of the various bronchogenic diseases. An excellent bibliography is included in the book. The text is clearly written and the illustrations are really superb. The press work and the binding are well in keeping with the high standards of the publisher.

James T. Case, M.D.

Bronchus und Tuberkulose. By Dr. A. Huzly, Stuttgart-Gerlingen, and Dr. F. Böhm, Überruh/Isny. Cloth. Price, $13.55. Pp. 138, with 258 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1955.

This is a comprehensive clinical study on bronchial changes in pulmonary tuberculosis. The authors base their report on 1,500 patients in two large sanatoriums. The roentgenologic examination includes routine exposures in all projections, overpenetrated films, laminagraphy, and ample use of bronchography with both survey technique and topical studies. These procedures form the mainstay of the presentation without, however, making the book a mere roentgenologic atlas.

The presentation begins with bronchial changes, distortion, crowding, and dilatation caused by tuberculosis of the lung parenchyma without intrinsic tuberculous involvement of the bronchi. The changes also include kinking, stricture, and bronchiectasis. Another section considers the relation of lymph node tuberculosis and bronchus, analyzing compression of and perforation into the bronchus, with reference to recent discussions on the numerical significance of these perforations. The authors report an incidence of 2.6 per cent florid fistulas and 8.1 per cent scars after perforation, in their material. This over-all of 10.7 per cent compares well with other series in adult tuberculosis. In children values up to 23 per cent have been reported. Lymphonodular tuberculosis, possibly demonstrable by laminagraphy, may lead to swelling of the bronchial mucosa and hemoptysis several weeks prior to gross compression or perforation. This section is particularly well illustrated by colored bronchoscopic images and diagrams, in addition to roentgenograms.

Other chapters deal with distortion of the bronchial tree by extrapulmonary changes such as pleurisy, pleural scars and plastic surgical intervention, and with bronchial tuberculosis proper.

The diagnosis is documented in all cases by bacteriologic or pathologic data. No attempt at roentgenologic differential diagnosis is made. The material is presented in the form of case reports with ample illustrations. Each chapter is introduced by the thesis and closed by a thorough discussion. An extensive "international" bibliography is appended. The entire volume is informative for the phthisiologist and radiologist.

Felix G. Fleischner, M.D.

Die Lungentuberkulose; Diagnose und Therapie. Von Prof. Dr. Med. P.-G. Schmidt, Waldbreitbach. Third edition. Cloth. Price, DM 58.-. Pp. 384, with 234

illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1956.

Even though the tuberculous pandemy has undergone a spectacular postwar decline, the "accepted" methods of antituberculous therapy are still changing at an incredible pace. Owing to delay in publication, ever so often a panel discussion, which establishes a "new" procedure, appears in print at a date when the praised procedure has become obsolete. Similarly, the second edition of Schmidt's textbook on tuberculosis, written in 1947, was outdated (by his own admission) at the time of publication, late in 1948. The radiologist cannot remain indifferent to these changes, because at times he must face a chest roentgenogram with lucite balls, intrapleural oleothorax, or extraperiosteal paraffin pack, under which circumstances well trained but inadvertent observers have been known to offer exhilarating interpretations.

The material in this third edition is by necessity condensed, but fairly well balanced. After introductory chapters on bacteriologic, pathologic, and other topics, there follows a section on diagnosis, which devotes a relatively limited space to the roentgenologic examination, compensated by profuse illustrations of the text with well-captioned reproductions. A single drawing of pulmonary segments is inserted between the subsections on percussion and auscultation. Koch's antiquated subcutaneous tuberculin test is described, but there is no mention of purified protein derivative (PPD). Only brief remarks on functional respiratory tests are included. An otherwise well documented clinical study of pulmonary tuberculosis, with sections on endobronchial lymph node perforation and bronchial tuberculosis, lists Boeck's sarcoidosis as a "sclerosing miliary tuberculosis."

The part devoted to antituberculous treatment has several objectionable features. Tuberculin therapy, in conjunction with antibiotics, is recommended in torpid forms, ultraviolet rays "are good for" pleuritic residuals and "other inactive" conditions, and roentgen therapy (5–10 per cent of one TED, ports of 10–12 cm^2, filter 4 mm. Al or 1.0 mm. Cu, fortnightly irradiations) is suggested for its fibrosing effect. There is a substantial chapter on tuberculostatics and antibiotics, though perhaps too much confidence is being placed in conteben and other sulfa compounds. The section on surgery discusses percutaneous puncture and instillation of cavities, Monaldi's drainage, Maurer's speleostomy, interventions on the phrenic nerve, and extrapleural pneumolysis with paraffin pack or with oleothorax, procedures which are now seldom, if ever, used in this country. Undisguised nostalgia pervades the chapters on artificial pneumothorax, and to a lesser extent on pneumoperitoneum, and on the classical thoracoplasty. Only brief mention is made of the "extramusculo-periosteal paraffin plombage" which is certainly less radical, and better tolerated, than the extensive removal of ribs. At the end of the section, satisfactory coverage is given to pulmonary resection and to decortication.

The author's clear presentation, facilitated by the excellent quality of the paper, print, and reproductions, makes for easy reading. Altogether, this is an adequate summary of what the last decades have accumulated in phthisiologic knowledge. Perhaps subconsciously, the author, like many other good practitioners, refuses to accept the shotgun type of therapeutic approach fostered by the success of the antibiotics. The multitude of procedures presented in this book would impose the need for a master clinician, capable of selecting the best one in any given instance. On the other hand, perhaps all these procedures are outlined for the sake of completeness. Many of the methods included in the test, however, are not only inefficient, but often deleterious (unilateral phrenico-exeresis can decrease respiratory function by as much as 30 per cent).

This book is therefore not recommended for the uninitiated, but it may provide the specialist with fine, practical points, coming from Schmidt's extensive personal experience. For the radiologist, perusal of this volume is a satisfactory review of the varied types of chest surgery to which tuberculous patients have been subjected in the recent past.

E. R. N. Grigg, M.D.

Principles of Chest X-Ray Diagnosis. By George Simon, M.D., F.F.R., Assistant Director, X-ray Department, Brompton Hospital, London; Radiologist, St. Bartholomew's Hospital, London; Demonstrator, Radiological Anatomy, St. Bartholomew's Hospital, London. Cloth. Price, 50s. Pp. 183, with 162 illustrations. F. A. Davis Company, 1914 Cherry Street, Philadelphia 3, Pennsylvania, 1956.

The most interesting feature of this new text is its unusual organization. The author, believing that an observer's first obligation is to

describe findings accurately, and only then to correlate and interpret them, has arranged his subject matter according to the appearance of roentgenographic shadows rather than according to clinical disease entities. Thus he considers in succession "homogeneous shadows," "linear shadows," "high density shadows," and "hypertranslucencies."

The first of these chapters treats of effusions and of consolidations and atalectases. The characteristics of these latter lesions as they affect the various lobes and bronchopulmonary segments are described in detail. Also included here are mass lesions and processes producing miliary shadows. The differential diagnosis of these lesions is discussed and helpful tables of etiologic agents are presented.

Included in the discussion of linear shadows are processes such as pleural thickening; lymphatic dilatation; parenchymal scars; dilated bronchi; cavities, bullae, and cysts; and lesions producing so-called "honey-combing." Under "high density shadows," calcified lesions, hemosiderosis, and opaque foreign substances are described. The characteristics of various forms of emphysema occupy most of the section on hypertranslucencies.

In addition to the sections cited above, the volume contains chapters on cardiovascular abnormalities, mediastinal and diaphragm shadows, the bones and soft tissue coverings of the thorax, and finally a section on remote bone changes associated with pulmonary disease. Also included is a commendable section, "The Time Factor in X-Ray Diagnosis and Comparison of Radiographs of Different Dates," in which the author discusses the timing of serial roentgenograms in tuberculosis and following acute pneumonias and various surgical procedures. A routine for the comparison of serial films is proposed and findings of particular importance, together with their clinical significance, are tabulated.

The indications for bronchography and laminagraphy and the techniques of these specialized procedures are considered at length, while the discussion of more standard techniques is limited principally to positioning. The selection of radiographic factors is dismissed with the debatable statement, " . . . it is best to use a value of kilovolts which will give the degree of contrast in the radiograph best suited to the particular observer."

The text is concise, well written, and illustrated with reproductions of excellent quality. The author has succeeded admirably in his stated purpose of writing a book for the student radiologist and the clinician who is particularly concerned with chest diseases. It is not an encyclopedic text, however; the bibliography is meager; and though it is well indexed, because of its unusual organization, the radiologist will find it a reference work of limited value.

WILLIAM J. TUDDENHAM, M.D.

DISEASES OF THE CHEST. By H. Corwin Hinshaw, M.D., Ph.D., Clinical Professor of Medicine, Stanford University School of Medicine; and L. Henry Garland, M.B., B.Ch., Clinical Professor of Radiology, Stanford University School of Medicine. Cloth. Price, $15.00. Pp. 727, with 634 illustrations. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania, 1956.

A scholarly, concise, up-to-date presentation of all aspects of chest disease has been prepared by Dr. Hinshaw and Dr. Garland, both well known authorities in their fields of internal medicine and clinical radiology. It is a pleasure to see all recent advances in this field brought together in one volume. The most modern aspects of antibiotic, anticoagulant, antiparasitic, and antimycotic therapy for the various chest conditions are presented. Detailed description of clinical manifestations, laboratory findings, and roentgenologic interpretation is given in each instance, thereby making this not only an excellent textbook for students initially learning the subjects, but also a comprehensive desk reference book for practicing physicians and radiologists.

The initial hundred pages are devoted to detailed diagnostic procedures, segmental pulmonary anatomy, and pulmonary physiology. The heart is discussed only as it relates to pulmonary physiology and disease. Roentgenograms are generally small but numerous, and they adequately illustrate conditions discussed. A large section of the book relates to pulmonary tuberculosis and the most modern aspects of its treatment. Bibliographies are not cumbersome and they include the latest 1955 references. This book is highly recommended as a valuable addition to the bookshelf of every practicing physician.

ARCH H. HALL, M.D.

BOOKS RECEIVED

Twenty-First Semiannual Report of the Atomic Energy Commission. By United States Atomic Energy Commission. Paper. Pp. 396, with illustrations and tables. United States Government Printing Office, Washington, D. C., 1957.

Intestin Grêle Colon-Rectum. By Guy Albot, Médecin de l'Hôtel-Dieu; and F. Poilleux, Chirurgien de l'Hôpital Corentin-Celton. Paper. Price, 3.400 fr. Pp. 362, with 168 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1956.

Studies on the Distribution of Tritium-Labelled Dihydrostreptomycin and Tetracycline in the Body. Acta radiologica, Supplement 142. By Torsten André. Paper. Price, Sw. Kr. 25:-. Pp. 98, with 41 illustrations. Acta radiologica, Stockholm 2, Sweden, 1956.

The Measurement of Body Radioactivity. Paper read at a Conference held at Leeds on April 16–17, 1956. British Journal of Radiology, Supplement 7. Paper. Price, 25 s. Pp. 130, with numerous illustrations and tables. British Institute of Radiology, 32 Welbeck Street, London, W.1, England, 1957.

Principles of Urology; An Introductory Textbook to the Diseases of the Urogenital Tract. By Meredith F. Campbell, M.S., M.D., F.A.C.S., Emeritus Professor of Urology, New York University. Cloth. Price, $9.50. Pp. 622, with 319 illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

Positioning in Radiography. By K. C. Clark, M.B.E., F.S.R., University of London, British Postgraduate Medical Foundation. Seventh edition. Cloth. Price, $29.00. Pp. 655, with 2,150 illustrations. Intercontinental Medical Book Corp., 381 Fourth Avenue, New York 16, New York, 1957.

Current Therapy—1957; Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D. Cloth. Price, $11.00. Pp. 731. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

A Radiologic Study of the Brain Circulation by Rapid Serial Angiography of the Carotid Artery. Acta radiologica, Supplement 140. By Torgny Greitz. Paper. Price, Sw. Kr. 30:-. Pp. 123, with 28 illustrations. Acta radiologica, Stockholm 2, Sweden, 1956.

Actions Chimiques et Biologiques des Radiations. Edited by M. Haissinsky. Second series. Cloth. Price, 3.400 fr. (Paper. Price, 2.800 fr.) Pp. 222, with 39 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1956.

Roentgen Changes in the Cranium in 153 Intracranial Tumours in Children Aged 0–15 Years. Acta radiologica. Supplement 141. By Helge Hertz and Thomas Rosendal. Paper. Price, Sw. Kr. 30:-. Pp. 54, with numerous illustrations. Acta radiologica, Stockholm 2, Sweden, 1956.

Rectoscopie, Sigmoïdoscopie. By P. Hillemand, R. Cattan, A. Lambling, and A. Bensaude. Third edition. Cloth. Price, 7.400 fr. Pp. 270, with 127 figures and 39 color plates. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, 1956.

Guide Technique et Topographique d'Exploration Bronchologique (Bronchoscopie et Bronchographie). By Jean Ioannou, Médecin-adjoint au Sanatorium de Chivilly, Attaché de Bronchoscopie à la Clinique de Pneumo-phtisiologie de la Faculté de Paris; in collaboration with A. Duchet-Suchaux and A. Pinelli. Paper. Price, 1.400 fr. Pp. 114, with 66 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1956.

La Polyarthrite Chronique Évolutive. By L. Isemein, Médecin des Hôpitaux de Marseille, and A.-M. Fournier, Médecin Électro-radiologiste des Hôpitaux de Marseille; with the collaboration of P. Ciaudo, A. Trifaud, and Cl. Courtieux. Paper. Price, 3.200 fr. Pp. 316, with 192 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1956.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Blount, Henry C., Jr. Localized mesothelioma of the pleura; a review with six new cases. *Radiology*, Dec., 1956, *67*, 822–834. (Address: 1040 Delaware Ave., Marion, Ohio.)

The literature on localized mesothelioma of the pleura is briefly reviewed and 6 new cases are presented. This brings the number of cases reported in the English literature to approximately 55.

Some of the reported cases of mesothelioma of the pleura have been entirely asymptomatic. Others had mild cough and a feeling of heaviness and vague discomfort in the chest. Dyspnea, weight loss, malaise and chest pain were present in some. Hypertrophic pulmonary osteoarthropathy was present in a number of the patients. Others showed clubbing of digits. Growth of the neoplasm was relatively slow in most instances. Both benign and malignant forms of localized mesothelioma have been reported.

Localized mesotheliomas of the pleura may be seen roentgenologically at any visceral pleural site over the lung surface or in any interlobar fissure, or at any parietal pleural site over the chest wall, mediastinum, or diaphragm. The masses are generally discretely outlined, but the outline may be obscured by pleural effusion. Mesotheliomas at the surface of the lung usually have the roentgenographic appearance of extrapulmonary masses, but occasionally movement with the lung during respiration can be demonstrated. Tumors often are elongated and roughly lenticular in outline.

Five of the reported cases were of the benign fibrous type. One was a benign localized epithelial mesothelioma showing papillary projections, with fibrovascular stalks, covered with mesothelial cells not unlike epithelial cells in appearance.—*Arno. W. Sommer, M.D.*

Ovenfors, Carl-Olof. Venous communications between the cardiac veins and the large venous trunks in the superior part of the mediastinum. *Acta radiol.*, Sept., 1956, *46*, 518–522. (From: The Roentgendiagnostic Department of the Paediatric Clinic, Karolinska Sjukhuset, Stockholm, and the Roentgen Department of the Paediatric Clinic, Sahlgrenska Sjukhuset, Gothenburg, Sweden.)

The author reports a very interesting case of visualization of a previously unreported mediastinal vascular network communicating with the coronary sinus system. The films of this case illustrate the communication of the cardiac veins with the left innominate vein via the first intercostal vein on the left and the superior vena cava on the right.

With additional study on 11 autopsy cases, it was possible to confirm this vascular network extending from the coronary sinus system to the left innominate vein via the first intercostal vein on the left and the superior vena cava on the right in 9 cases. There was no evidence of extravasation in any of these cases indicating a direct flow through veins. As a plexus cannot be demonstrated by filling of the large veins in the superior part of the mediastinum, it is presumed that the flow through this area is inappreciable under normal conditions. It is postulated that the anterior mediastinal vascular plexus serves as a collateral circulation in the presence of impediment in emptying of the cardiac veins.—*Thomas D. Allison, M.D.*

Schorr, S., Rosenberg, S. Z., Eliakim, M., and Braun, K. Relationship of roentgenographic findings to hemodynamics in mitral stenosis. *Radiology*, Dec., 1956, *67*, 815–821. (Address: S. Schorr, Hadassah University Hospital, Jerusalem, Israel.)

In this investigation the authors have attempted to determine the relationship of the size and appearance of the pulmonary artery, the lung fields, and the various heart chambers as seen roentgenologically to the hemodynamic data obtained by cardiac catheterization in 50 cases of mitral stenosis. These studies were carried out because it was realized that if it were possible to estimate the degree of pulmonary hypertension by roentgenographic examination of the heart and lungs, great service could be rendered to the clinician and cardiac surgeon.

It was found that moderate or marked enlargement of the pulmonary artery and the hilar markings was accompanied by elevated pulmonary artery mean pressure, and pulmonary vascular and arteriolar resistances. The tendency was to an inverse relation between these roentgen findings and the hemodynamic data. It was also noted that moderate or marked enlargement of the heart was accompanied by increased pulmonary and right ventricular mean pressures and pulmonary vascular resistance. Increase in heart size was accompanied by a decrease of cardiac index. Enlargement of the left atrium was always associated with elevated pulmonary "capillary" mean pressure. In a few instances mild enlargement of the left atrium was accompanied by extremely high pulmonary "capillary" mean pressure.

The appearance of the peripheral lung fields did not correlate well with the pulmonary artery and "capillary" mean pressures and pulmonary arteriolar resistance. The authors state that normal peripheral lung fields were sometimes found in patients with severe pulmonary hypertension.—*A. Ralph Watson, M.D.*

Abdomen

Wang, C. C., and Petersen, James A. Malignant lymphoma of the gastrointestinal tract: Roentgenographic considerations. *Acta radiol.*, Sept., 1956, *46*, 523–532. (From: De-

partment of Radiology, Massachusetts General Hospital, Boston, Mass.)

The authors present a review of 165 cases of malignant lymphomatous involvement of the gastrointestinal tract. They note that these gastrointestinal cases represent approximately 10 per cent of all the lymphoma cases admitted to their general hospital. Of this group 66 had roentgen studies available. The site of the lesion in 4 cases was esophageal, in 48 gastric, in 12 in the small intestine and in 2 in the large intestine. The lesions exhibited a variety of roentgenographic patterns mimicking a variety of organic lesions. It is felt by the authors that based on roentgen examination alone a differentiation between carcinoma and solitary lymphoma of the esophagus or colon cannot be made.

In the stomach, however, the diagnosis may be suggested. The unusual roentgen findings in the stomach in malignant lymphoma include (1) extensive involvement with paucity of clinical complaints, (2) extreme widening of the gastric folds, (3) stiffening and thickening of the gastric wall without undue interference with peristalsis and (4) extension of the lesion through the pylorus to involve the base of the duodenal bulb in some cases.

In lymphoma of the small intestine which represented 36 per cent of the cases in this series a distinctive roentgen finding is the presence of multiple, ulcerated lesions with relatively normal intervening mucosa, without intestinal obstruction. The authors note that, when the involvement of the gastrointestinal tract is part of a long standing generalized process, diagnosis may be readily established.—*Thomas D. Allison, M.D.*

ARNETT, NORMAN L., and FRIEDMAN, PAUL S. Lymphangioma of the colon: Roentgen aspects; a case report. *Radiology*, Dec., 1956, *67*, 882–885. (Address: N. L. Arnett, 1422 Chestnut St., Philadelphia 2, Pa.)

The authors report a case of lymphangioma of the colon to add to the 9 cases of this disease of the gastrointestinal tract that have appeared in the English literature. Described for the first time are some distinctive roentgen characteristics which may suggest the diagnosis.

The demonstration and visualization of this tumor are difficult due to its variable contour and cystic nature with the fluid readily passing between its thin internal septa. It is best seen when the colon is partially distended with barium as it disappears when the colon is fully distended and compressed. The mass is sharply marginated, peripheral in location, and round or oval in shape. Overlying intact mucosa indicates its intramural location. Other benign tumors which may exhibit similar roentgen characteristics are cavernous hemangiomata and lipomata.

Lymphangiomata are thought to originate in the lymphatic plexus within the submucosa. The cause of their development is not known, but the supposition that seems most plausible is that the mesenteric lymph nodes are obstructed, with a subsequent stasis and dilatation of the lymph vessels due to a rise in pressure within the lymph nodes.

A case report is presented in which a lymphangioma of the ascending colon was found.—*D. N. Dysart, M.D.*

HJORTH, POVL. Cholangiography by the biligrafin method with or without preceding oral cholecystography; an attempt to assess the reliability of the biligrafin method. *Radiology*, Dec., 1956, *67*, 835–839. (Address: Copenhagen Municipal Hospital, Copenhagen, Denmark.)

The author reports on 270 cholangiographic studies with biligrafin (cholografin) which were performed in the Department of Radiology of the Copenhagen Municipal Hospital from November, 1953 to January, 1955. In 237 cases there had been failure to visualize the gallbladder by oral cholecystography, and in 33 cases the intravenous method was used primarily in previously cholecystectomized patients. This examination was not attempted if the icterus index was over 20 since there were several instances of nonvisualization when the index was abnormally high.

Side effects from the medium were observed in 27 patients. In only 10 (3 per cent of the entire series), were they severe enough to prevent completion of the examination.

Results were grouped as follows: (1) Normal common duct and normal gallbladder, 21 cases; (2) normal common duct, nonvisualized gallbladder, 139 cases; (3) dilated common duct, 41 cases; (4) no visible excretion, 51 cases; (5) unsatisfactory examination due to various causes, 8 cases; and (6) incomplete examination because of reactions to the medium, 10 cases.

A discussion which shows good correlation between the roentgen and operative findings is presented. The results suggest that failure to visualize the gallbladder at the time that successful visualization of biliary ducts is achieved following injection of biligrafin indicates severe changes of the gallbladder, cystic duct, or both, with mechanical obstruction to the entrance of the opaque medium. In several cases, nonvisualization of the gallbladder by the oral method was followed by distinct visualization when the intravenous technique was used. It is thought that the reason for this is that the concentrating power of the gallbladder wall is impaired or absent due to disease and the fact that the gallbladder becomes visualized following biligrafin injection does not mean the gallbladder is normal. In most of the cases where there was no visible excretion of biligrafin, the icterus index and liver function tests were normal indicating that a cholecystitis-cholangitis was present.

The author feels that with intravenous cholangography more information can be gained about the gallbladder and bile duct system when routine and repeat oral cholecystographies show a nonvisualized or poorly visualized gallbladder.—*D. N. Dysart, M.D.*

Berlin, Herbert S., Poppel, Maxwell H., and Stein, Joseph. Intravenous cholangiography: Pitfalls in interpretation. *Radiology*, Dec., 1956, *67*, 840–844. (Address: H. S. Berlin, Radiology Service, VA Hospital, Bronx 68, N. Y.)

The authors discuss several pitfalls which might interfere with the correct interpretation of intravenous cholangiographic studies and the means for their avoidance.

Small radiolucent calculi may be masked by the dense opacification occasionally produced by cholografin. Overlying shadows of the liver, kidney and loops of small intestine which may contain some opaque material may produce deceiving images. The renal excretion of cholografin may simulate the bile passages, particularly if the renal pelvis should be bifid and the upper calyceal system lies on or near the same plane as the bile ducts. The stratification phenomenon produced when cholografin fails to mix with the bile and gravitates to the dependent portion of the gallbladder produces a circular radiolucent shadow suggesting a large lucent stone or free gas within the gallbladder.

Procedures which the authors have found helpful to lessen those pitfalls, include a routine oral cholecystographic examination in noncholecystectomized patients prior to the intravenous study, in order to provide a functional evaluation and baseline study of the gallbladder. Laminagraphy will help to eliminate obscuring gas and organ shadows. The underlying renal collecting system can be separated from the biliary tree by utilizing right posterior oblique views. The stratification effect may be removed by means of a fatty meal stimulus which will break up the layering or avoided by ingestion of a fatty meal approximately one hour prior to the examination.

Two case reports are presented and many roentgenograms are reproduced to illustrate the discussion.—*D. N. Dysart, M.D.*

Gynecology and Obstetrics

Schwarz, Gerhart S., Kirkpatrick, Rob H., and Tovell, Harold M. M. Correlation of cephalopelvimetry to obstetrical outcome with special reference to radiologic disproportion. *Radiology*, Dec., 1956, *67*, 854–862. (Address: G. S. Schwarz, 622 West 168th St., New York 32, N. Y.)

The correlation of roentgen cephalopelvimetry by the Ball method to obstetrical outcome was determined by charting obstetrical results and roentgen measurements on graphs. It was found that the method of Ball produces roentgen predictions with an accuracy of 90 per cent or better, except when mid-pelvic disproportion is present. The use of an orthometric view to obtain a more reliable measurement of the interspinous diameter appears from a preliminary survey to give at least a 10 per cent improvement in accuracy of predictions at the mid-pelvis.

The graph method of charting measured cases made it possible to arrive at the following roentgenometric classification of cephalopelvic disproportion in which the Ball method gives the best results:

For the Inlet: (A) "No Disproportion": All cases in which the volume of the fetal head is smaller than or equal to the volume capacity of the inlet; (B) "Boderline Disproportion": All cases in which the volume of the fetal head exceeds the volume capacity of the inlet but by not more than 70 cc.; (C) "High Disproportion": All cases in which the volume of the fetal head exceeds the volume capacity of the inlet by more than 70 cc.

For the Mid-Pelvis: (A) "No Disproportion": (1) All cases in which the volume of the fetal head is smaller than or equal to the volume capacity of the bispinous diameter. (2) All cases in which the volume of the fetal head is larger than the volume capacity of the bispinous diameter but does not exceed it by more than 90 cc.; (B) "Borderline Disproportion": All cases in which the volume of the fetal head exceeds the volume capacity of the bispinous diameter by more than 90 but not more than 220 cc.; (C) "High Disproportion": All cases in which the volume of the fetal head exceeds the volume capacity of the bispinous diameter by more than 220 cc.

Certain deficiencies have become apparent: (1) The method is less accurate at the mid-pelvis than at the inlet; (2) the method is less accurate in the presence of disproportion than in its absence; and (3) the number of cases falling into a roentgenologic borderline group is too large at the mid-pelvis. Despite these deficiencies, the results with the Ball method compare favorably with those obtained with the method of Chassar Moir or that of Caldwell, Moloy, and Steer.—*Harold C. Hamilton, M.D.*

Genitourinary System

Ransom, Charles L., Landes, Ralph R., and McLelland, Robert. Air embolism following retroperitoneal pneumography: A nationwide survey. *J. Urol.*, Nov., 1956, *76*, 664–670. (Address: C. L. Ransom, 776 Main St., Danville, Va.)

The authors have reviewed the literature, and added one case of their own in which embolism was a cause of death following presacral retroperitoneal pneumography. As a result of their survey, they find that 58 deaths and 64 severe nonfatal reactions to gas emboli have resulted from retroperitoneal pneumography. In general, the presacral route ap-

pears to be the less hazardous method of injection, and carbon dioxide, because of its solubility, is recommended as the best contrast medium for retroperitoneal pneumography. Although there is universal agreement that the patient should be placed in the left side down position whenever the first sign of difficulty occurs, at least 2 of the patients in this series died in spite of this particular maneuver. Five of the nonfatal cases, all which were injected by the presacral route, were thought to have been saved by rotating the patient to the left side down position.

One illustration and 5 charts are included.—*George W. Chamberlin, M.D.*

GRAVES, F. T. The anatomy of the intrarenal arteries in health and disease. *Brit. J. Surg.*, May, 1956, *43*, 605–616. (From: King's College Hospital, London, England.)

A beautiful and intricate study of the intrarenal arteries and veins is presented utilizing colorful plastic casts and arteriograms. On the basis of arterial distribution, the renal parenchyma is divided into 5 segments—the apical, upper, middle, lower and posterior—each of which is supplied by its own artery. The mainstem of the renal artery divides into an anterior and a posterior branch before entering the hilum. The upper, middle, and lower segments arise from the anterior branch, while the posterior segment comes directly from the posterior branch. The artery to the apical segment arises usually from the anterior branch, but it may also arise from the upper segment artery, the mainstem artery, the aorta itself, or even the posterior branch.

Many experiments have proved that there is no collateral arterial circulation between renal segments. In contrast, the intrarenal veins anastomose freely. The main venous trunks vary from 1 to 4 in number, and they are interconnected by a series of arcades.

Many of the so-called accessory or aberrant arteries are in fact normal segmental arteries whose origin from the mainstem is precocious. This is important since the ligation of a vessel on the grounds that it is accessory will lead to necrosis of a segment or part of a segment. In 63 per cent of normal kidneys the artery to the lower segment has the most proximal origin, arising from the anterior branch, the mainstem artery, or even the aorta itself.

A differentiation between renal cyst and neoplasm is often possible by arteriography. With cysts there is no diminution of the vascular supply, except for the avascular area occupied by the cyst itself. The normal cortical pattern with glomerular "boutons" extends right up to the edge of the cyst. In a neoplastic renal disease, one or more segmental branches will be absent and the arterial supply to the tumor area diminished. There may be pooling of the contrast medium about the periphery, and smaller segmental branches are arranged about the tumor like "grasping fingers." In advanced cases, there may be no recognizable pattern due to intrarenal spread by way of the freely anastomosing venous channels.

A study of the segmental arterial distribution in calculus disease showed very little disturbance in the arrangement of the intrarenal arteries. Even with marked hydronephrosis and staghorn calculi, the segmental arteries were not displaced or reduced in caliber. However, the finer cortical arteries were extremely frail, elongated, and tortuous when compared to the normal.

Finally, the author discusses renal aortography at operation using specially designed needles, and a 3 by 5 inch waterproof film pouch, which is slipped into the wound behind the kidney. This technique had been used on 5 occasions successfully, but it is still in the experimental stage.—*Arch H. Hall, M.D.*

BURKE, DONALD E. Isotope radiographs for localization of renal calculi during surgery: A new truly portable radiographic unit using a radioisotope (thulium 170) as an energy source. *J. Urol.*, Nov., 1956, *76*, 508–519. (From: Department of Surgery, Division of Urology, University of California Medical Center and the Urology Section, Veterans Administration Hospital, Los Angeles, Calif.)

The author reports a new completely portable, lightweight, radiographic unit containing the radioisotope thulium 170 for use in the assisting of the operative removal of renal calculi. This unit has many advantages over ordinary roentgen-ray equipment in the operating room. In addition to its mobility and small size, it eliminates the explosion hazard. The initial cost is said to be low. The disadvantages associated with such a unit are the lack of fine detail associated with a short focal film distance and the relatively large size of the source, particularly when held in the hands of the operator. However, for gross lesions in tissues of small or moderate density the unit is quite satisfactory as shown by the author's experience.—*George W. Chamberlin, M.D.*

BOREHAM, PETER. The surgical spread of cancer in urology. *Brit. J. Urol.*, June, 1956, *28*, 163–175. (From: St. Mark's Hospital, London, England.)

The author has compiled a series of 29 cases of probable metastases from carcinomas of the urinary tract. Transitional cell tumors can be shown to shed malignant cells into the urine with varying profusion and frequency. Although natural implantation of malignant cells is known to occur, it is doubtful whether this method accounts for the spread of transitional cell tumors down the ureter or across the bladder, unless there is some break in the mucous membrane or some area of granulation tissue.

This series included 6 cases of recurrence of carcinoma of the bladder occurring in the urethra and 5

cases where it occurred in a prostatic bed after prostatectomy had been performed in the presence of bladder carcinoma. The other 15 cases had recurrence in the scar of an open operation. After approximately 5 per cent of open operations on the bladder, the first recurrence was in the scar. Surgical implantation does occur and may spoil an otherwise curative operation.

To minimize the risk of urethral implantation, the author urges extreme gentleness during all instrumentation using utmost precautions to avoid abraiding the urethral mucosa. If there is prostatic obstruction associated with bladder carcinoma, the latter condition should be treated first, if at all possible. If both procedures are necessary concomitantly, then it is advised to omit sutures usually placed to assist hemostasis and trigonization of the bladder neck behind. The postoperative follow-up should be more careful than usual, and the urethrascope should be freely used. To prevent scar implants the bladder should be well irrigated, just prior to cystotomy, in order to wash out all malignant cells in the urine and any spill of urine when the bladder is opened should be avoided. The use of towels about the bladder incision itself is recommended. Careful postoperative scrutiny of the scar with an eye to early discovery and excision of any recurrence is suggested. An appreciation of the frequency of surgically induced implant metastasis may lead to more cautious and meticulous surgical procedures.—*Arch H. Hall, M.D.*

Nervous System

Brain, Russell. (London, England.) Some aspects of the neurology of the cervical spine. *J. Fac. Radiologists*, Oct., 1956, *8*, 74–91.

Congenital abnormalities of the cervical spine include: (1) Basilar impression; (2) occurrence of an occipital vertebra; (3) occipito-atlantal fusion (assimilation or occipitalization of the atlas); (4) deformities of the foramen magnum; (5) malformations of the axis, especially those leading to atlanto-axial dislocation; (6) cervical spina bifida; (7) the Klippel-Feil syndrome; and (8) miscellaneous abnormalities, including cervical ribs.

The congenital abnormalities tend to be multiple. It is necessary to distinguish those neurologic syndromes which are the effects of the congenital abnormalities upon the nervous system from congenital abnormalities of the nervous system itself, which are the results of the same tendency to developmental error which produced the bony abnormalities. There is no constant correlation between one type of bony abnormality and one type of neurologic abnormality.

Occipitalization of the atlas has occurred in association with other abnormalities, but does not appear to have been responsible for symptoms in itself. Basilar impression may be the result of a congenital abnormality, or it may be due to one of several bone diseases. Various roentgenologic measurements (Chamberlain, McGregor, Bull, *et al.*) are discussed. The Arnold-Chiari malformation occurs chiefly in 3 circumstances: (1) Usually in infancy associated with spina bifida and a myelomeningocele, often with hydrocephalus; (2) associated with primary basilar impression; and (3) as the sole abnormality. The Klippel-Feil abnormality is often associated with the Sprengel shoulder, or it may be associated with cervical ribs. In lesions of the odontoid process, it is convenient to use the term "atlanto-axial dislocation" to cover all displacements of one bone or the other. Included in such lesions are: (1) Dislocation secondary to the spread of infection in the atlanto-axial articulation; (2) traumatic atlanto-axial dislocation due to rupture of the transverse ligament; and (3) atlanto-axial dislocation due to interruption of the odontoid process because of (a) simple odontoid fracture, (b) apophysiolysis prior to age of three years, (c) congenital absence, (d) failure of union of the odontoid process with the rest of the axis, or (e) abnormal laxity of the transverse ligament in association with assimilation of the atlas. In simple atlanto-axial dislocation there is slipping of moderate degree between atlas and axis in two parallel planes, and abnormal mobility is reduced to a minimum when the head is flexed. However, when the odontoid process is separated and the head is flexed, the dislocation between atlas and axis is more severe than in simple atlanto-axial dislocation. The atlas slips forward and downward, so that its plane makes with the plane of the axis a progressive angle open upward and backward. When the transverse ligament is ruptured, the odontoid process moves laterally together with the axis, but when the odontoid itself is fractured, it is fixed to the atlas by the transverse ligament and consequently follows the displacement of the atlas.

Neurologic symptoms resulting from atlanto-axial dislocation may occur many years after the etiologic trauma. If there is clear roentgenographic evidence of a congenital abnormality in the occipito-atlantal region, the myelopathy may be presumed to be a delayed effect of the congenital abnormality on the function of the medulla and spinal cord. Otherwise, there may be no way of deciding whether the initial lesion was an odontoid fracture, or whether the injury caused trouble only because of a pre-existing congenital abnormality.

Neoplasms of the cervical spine are rare. Involvement may be due to metastasis, as from carcinoma, or it may be due to a primary lesion such as neurofibroma.

In cervical spondylosis it is the osteophytes which are the chief cause of symptoms. Not all degenerated disks are the site of osteophytes, and hence, disk degeneration in itself is not necessarily a cause of symptoms. In roentgenograms of a patient with cervical spondylosis, chief attention should not be directed to narrowing of the intervertebral disk

spaces, but to the presence or absence of an opacity projecting into the spinal canal from the posterior end of the disk space, and associated with sclerosis of the adjacent portions of the vertebral bodies. When posterior osteophytes are readily recognizable and correspond in position to the level of the symptoms, it will often be unnecessary to do a myelogram. Cervical myelopathy may be more extensive than the area compressed, due to tension traction and interference with blood supply. It is a common observation that motor reflex and sensory functions of the spinal cord may be disturbed up to a segment or two higher than that which should be compressed by the highest disk protrusion. The same is true of radicular symptoms. A spinal root from any segment of the cervical enlargement may be compressed at more than one level of the spine either by a posterolateral protrusion of the intervertebral disk at the level at which it leaves the spinal cord or, usually at one vertebra lower, by an intraforaminal protrusion into the foramen through which it leaves the spinal canal. In addition, cervical spondylosis, by narrowing intervertebral disks, shortens the cervical spine. The spinal cord remains of the same length, and, hence, the position of the spinal roots within the intervertebral foramina must be affected, and they may be compressed against the lower border of normal intervertebral foramina.

In patients with cervical spondylosis a blow on the head, particularly one causing forcible extension of the neck, may cause severe and even irreparable damage to the cervical spinal cord. This is the result of complex factors which limit movement and tend to impair the blood supply of the cervical spinal cord in spondylosis.

In the cervical arthropathies there are bony changes in the cervical spine which closely simulate cervical spondylosis and therefore enter into its differential diagnosis. The author relates the case history of a woman with syringomyelia with secondary arthropathy of the cervical spine, which was severe enough at an early age to cause difficulty in diagnosis. The bony changes of a cervical arthropathy may be in themselves severe enough to add to the neurologic symptoms by compressing the spinal cord and nerve roots. Severe cervical arthropathy may occur also in tabes. A case is cited of a man with tabes of long standing who developed severe pains and increase in weakness of the upper extremities in spite of apparent adequate treatment of the tabes. Roentgen examination disclosed the gross bony changes of a cervical arthropathy. Such arthropathy associated with syringomyelia or with tabes may be severe enough to cause radicular symptoms by compressing the intervertebral foramina, or even spinal cord symptoms by compressing the cord itself.—*Samuel G. Henderson, M.D.*

Skeletal System

Brick, Edgar M. Vertebral osteophytosis; a clinical syndrome. *J.A.M.A.*, March 10, 1956, *160*, 828–829. (From: Orthopedic Service, Mount Sinai Hospital, New York, N.Y.)

The author defines vertebral osteophytosis as "an osteogenic proliferation occurring within the vertebral ligaments at their insertions into the apophyseal rings of the vertebral bodies." These ossific masses vary in size from that of a lentil to a large double plaque crossing the intervertebral space. This phenomenon represents a characteristic reaction to strain found at the insertions of powerful ligaments into bone at many sites throughout the axial and appendicular skeleton—along the iliac crests, at the femoral adductor tubercle, and at the insertion of the long plantar ligament into the calcaneus. The vertebral process is seen on roentgenograms as the so-called "lipping."

The condition is sometimes asymptomatic. When painful symptoms do occur, they are likely to return with variable intensity at intervals over a period of two to four years. Uncomplicated vetebral osteophytosis is self-limited, responds easily to rest and support, and only occasionally requires palliative measures.

The author emphasizes that this unique syndrome is not spinal arthritis, hypertrophic or otherwise, nor is it inevitably a mark of disk disease.—*William M. Loehr, M.D.*

Cusmano, Joseph V., Baker, David H., and Finby, Nathaniel. Pseudohypoparathyroidism. *Radiology*, Dec., 1956, *67*, 845–853. (Address: N. Finby, The New York Hospital, 525 East 68th St., New York 21, N. Y.)

The authors present 6 new cases of pseudohypoparathyroidism to add to the 30 now appearing in the literature. Diagnostic and roentgen features are emphasized.

Pseudohypoparathyroidism is a familial disease with 3 components: first, the metabolic defect, manifest as a failure to respond to parathormone; second, bone dysplasia; third, extraskeletal calcification and ossification. Symptomatology is predominantly related to episodes of hypocalcemia. Tetany, with muscular hyperexcitability, tonic convulsions, and muscle cramps, is seen at some time in every patient with this disease. Other findings are mental retardation, delayed and defective dentition, cataract formation and the characteristic round face and short stocky appearance. Commonly, the first, fourth and fifth metacarpals and the first and fifth metatarsals are short. The involved bones are frequently wider than normal. Metacarpal shortening is thought to be due to early closure of the involved epiphyses. Thickening of the calvarium was a prominent feature in the reported cases.

Extraskeletal calcification and ossification in the extremities have been reported in about two-thirds of the cases, usually in the vicinity of joints. In other forms of hypoparathyroidism the soft-tissue calcifi-

cations occur almost exclusively in the brain.— *A. W. Sommer, M.D.*

DUNLAP, KNOX, SWANSON, ALFRED B., and PENNER, RALPH S. Studies of the hip joint by means of lateral acetabular roentgenograms. *J. Bone & Joint Surg.*, Dec., 1956, *38-A*, 1218–1230. (From: Madigan Army Hospital, Fort Lewis, Wash.)

Studies were made of 400 hips by lateral roentgenograms of the acetabula by the following method:

The patient is seated with the thighs together and flexed to 90 degrees. The tube is placed parallel to the coronal plane of the body and the Bucky placed so the film is at right angle to, and centered beneath, the midline of the patient. The tube is tilted to form an angle of 30 degrees with the long axis of the body and centered over the iliac crest. Metal strip markers were used on the wooden seat to facilitate measurements of the pelvis.

The width of the pelvis was determined by measurements on the anteroposterior roentgenogram, and then the lateral roentgenogram was used to reconstruct a superior-inferior view of the pelvis.

A base line was drawn between the posterior acetabular margins and perpendicular lines erected from the intersection of this line with the posterior lips. Lines from this point across the anterior margin were drawn giving the angle of anterior obliquity of the acetabula.

The method was tested with skeletons and mechanical devices and the maximum error was found to be minus 10 degrees with the skeleton extended and plus 10 degrees with the skeleton flexed. The measurements closely approximated those of Le Damany who found the forward inclination of the acetabulum to be 35 degrees.

The authors found practically no variation in the angle of forward obliquity of the acetabulum in children of different ages. The average for children was 32 degrees and 35 degrees in the adult.

The anterior and posterior acetabular angles were also measured and the former averaged 50 degrees, and the latter 40 degrees in adults. With growth the acetabulum deepens, and the deepest point of the acetabulum shifts posteriorly, while the anterior angle increases, as compared to the posterior. The ilium and ischium contribute more to acetabular growth than the pubic bone.

The CA angle was also measured and found to be about 25 degrees in the infant, decreasing to 10 degrees in the adult. This angle shows the relationship of the head of the femur to the acetabulum with the hip flexed 90 degrees. It is obtained by erecting a line between the anterior and posterior acetabular lips with a right angle to the deep point of the acetabulum and a second line to the center of the head. The angle between these two is the CA angle.—*Martha Mottram, M.D.*

MAGILLIGAN, DONALD J. (Brooklyn, N. Y.) Calculation of the angle of anteversion by means of horizontal lateral roentgenography. *J. Bone & Joint Surg.*, Dec., 1956, *38-A*, 1231–1246.

The neck of the femur projects medially from the shaft forming the cervicofemoral angle, shaft-neck angle, or angle of inclination. It also projects anteriorly, forming the angle of anteversion.

Various methods have been devised, utilizing special devices for precise positioning and the true angle of anteversion determined by use of a formula.

The method presented by Magilligan embodies similar principles, but without the use of special positioning devices and graph is supplied to determine the true angle of anteversion.

The anteroposterior projection is taken with the femur held parallel to the table and in neutral position, so the dicondylar plane is parallel to the table; the cervicofemoral angle (angle α) is shown on this roentgenogram. The lateral roentgenogram is taken with the cassette held against the lateral side of the thigh and hip, parallel to the long axis of the femoral neck, after this is determined from the anteroposterior projection. The head of the tube is brought down between the thighs to the level required for the horizontal lateral roentgenogram. The cassette must be perpendicular to the tube. This roentgenogram shows the "projected" angle an anteversion (angle β). The true angle of anterversion (angle β') is determined by use of a graph or table in the article based on a trigonometric formula.

The degree of abduction or adduction can be varied so the cassette is parallel to the femoral neck in the lateral projection, which latter detail is essential to this method.

The true angle of anteversion is smaller than the projected angle. As the degree of varus increases, the discrepancy between β and β' is less marked and in valgus it is more marked.

A number of roentgenograms of models and cases are reproduced and the projected angles demonstrated.

The femoral line of reference used to calculate the angles may be difficult to draw accurately unless care is taken. It does not coincide with the center of the shaft, due to the configuration of the shaft. It is drawn from the center of the shaft at the junction of the shaft and neck to the center of the shaft at the level of the condyles.

With the necessary care, roentgenograms should be easy to obtain and to duplicate.—*Martha Mottram, M.D.*

MÜSSBICHLER, HERBERT. Arterial supply to the head of the femur; an arteriographic study *in vivo* of lesions attending fracture of the femoral neck. *Acta radiol.*, Sept., 1956, *46*,

533–546. (From: Roentgendiagnostic Department, Lasarettet, Falun, Sweden.)

The author reports the study of the arterial supply of the head of the femur by arteriographic methods *in vivo*. He demonstrates with excellent illustrations and anatomic studies the complete blood supply of the head of the femur and its particular relationship to aseptic necrosis of the femoral head. The author confirms with this work and a review of the literature that the capsular branches of the median circumflex artery provide the most important sources of blood supply to the femoral head. The ligamentum teres artery which may be wholly absent or obliterated plays a smaller part.

In this study the procedure was to inject the femoral artery percutaneously at the level of the inguinal ligament with 15 to 20 ml. of diiodone 50 per cent. Following this, 4 serial exposures were made in the next five to six seconds at a distance of 110 cm. A total of 28 diseased hips was studied, with comparison of the contralateral side in 19 cases. This group of cases included 4 with necrosis of the femoral head, 2 with pseudoarthrosis, 4 with Perthes' disease, 1 with metastatic carcinoma, 14 with fractures, and 1 with plastic procedure.

Emphasis is placed on the posterior collum branch of the medium circumflex artery and the inferior and superior synovial arteries in regard to their size and importance. It was found in the healthy hips that (1) contrast filling of the median and lateral circumflex arteries was practically equal irrespective of their variations in origin and course, and (2) contrast filling of the posterior collum branch visualized its course to the intertrochanteric arch. In the diseased hips contrast filling of the vessels revealed several local vascular changes which were interpreted as pathologic in that they were never noted in the healthy hip. These were (1) dilatation, (2) decreased rate of flow and (3) arrested circulation, forming 3 distinct types.

Although the author feels that these changes are pathologic, the number of cases is not sufficient to determine the relationship between these arteriographic changes and healing of fracture or the development of necrosis of the femoral head.—*Thomas D. Allison, M.D.*

Yentis, Irvan. The so-called solitary plasmocytoma of bone. *J. Fac. Radiologists*, Oct., 1956, *8*, 132–144. (From: X-Ray Diagnostic Department, The Middlesex Hospital, London, W.1, England.)

It has been suggested by some authors that a rare form of myeloma, the "solitary" plasmocytoma of bone, exists as a separate entity. This tumor has been regarded as benign, free from the risk of recurrence or dissemination and therefore curable by local surgery or roentgen therapy. The author examines this view critically by reference to 5 illustrative examples from cases of myelomatosis seen during the past twenty-five years. The criteria for selection as "solitary" plasmocytomata were: (1) Proof of diagnosis by histologic review; (2) a minimum of two years during which the lesion remained "solitary," (3) failure to show other lesions by serial roentgenologic examination of the skeleton; and (4) absence of Bence-Jones protein from the urine during the "solitary" phase.

The 5 cases described by Yentis indicate that it is possible for solitary tumors to remain localized for many years but eventually, in 4 of the 5 patients multiple lesions developed, only one, a sternal lesion being still a "solitary" lesion after ten years, nine months. In one case a second lesion appeared after ten years, in spite of upper thigh amputation, while a third lesion in this patient appeared after a further fourteen years, and death occurred twenty-six years after the finding of the initial "solitary" femoral tumor.

In follow-up observation one must consider roentgenologic, postmortem and time factors. It is well known that skeletal metastases from a primary carcinoma may not be demonstrated by roentgenography, and the same is true of the osteolytic lesions of myelomatosis. Even though no evidence of metastases is found in gross specimens at autopsy, it is obviously impossible to make microscopic examination of all tissues. It seems quite impossible from a time factor standpoint to say that such a tumor as a "solitary" plasmocytoma may exist, in view of fourteen years elapsing between the second and the third lesion in the case of Yentis above cited. Marrow biopsy may often refute the diagnosis of "solitary" myeloma of bone, several aspirations sometimes being required to prove the point.

Roentgenologically these lesions are usually found in the upper femur, ilium and vertebrae. They are osteolytic, arising in the medulla and involving the cortex by their outward spread. Roentgen therapy often causes calcification within the lesion. Yentis describes 2 roentgenologic varieties. The trabeculated type resembles an osteoclastoma, the lesion being traversed by a coarse meshwork of trabeculae and free from bone sclerosis or periosteal new bone formation. The nontrabeculated type may closely resemble a metastatic tumor as one from the breast, in that it is destructive lesion and nontrabeculated.

The author concludes that a plasmocytoma of bone is always part of a potentially malignant disease with unpredictable degrees of aggressive behavior. There are no clear-cut boundaries between the various forms of the disease, and the concept of a benign, unifocal, or "solitary" myeloma as a separate unrelated entity appears unjustified.—*Samuel G. Henderson, M.D.*

Medill, E. V. Primary reticulum-cell sarcoma of bone. *J. Fac. Radiologists*, Oct., 1956, *8*,

102–117. (From: Guy's Hospital, London, England.)

Primary reticulum-cell sarcoma of bone is a very radiosensitive malignant tumor which arises from the reticuloendothelial cells of the bone marrow in a single focus, and is capable of regional and distant metastases. It is most commonly found before the fourth decade. It has a predilection for the tubular bones of the lower extremity. Its clinical course is relatively long, with relative absence of the adverse systemic effects usually associated with an advanced malignant process.

Coley, Higinbotham, and Groesbeck in 1950 gave as the criteria for diagnosis the following: (1) Clinically the primary focus is in a single bone; (2) unequivocal histologic proof from the primary lesion and not from a metastasis; and (3) metastases present on admission only if regional or if the onset of symptoms of the primary tumor preceded the appearance of metastases by at least six months.

The author presents detailed clinical histories and roentgenographic illustrations of 9 cases of this disease. The first symptom almost always is pain of a dull aching character at the site of the lesion, intermittent, worse at night, not relieved by rest, and becoming progressively worse. The onset is insidious, coupled with general well-being of the patient.

Roentgen therapy produces almost dramatic subsidence of the tumor and reorganization of bone commonly occurs. The prognosis is much less gloomy than with other malignant bone tumors.

Pathologically, the tumor appears as a gray or whitish friable mass with gritty consistency, involving the medulla of the affected bone, penetrating and destroying the cortex and infiltrating the surrounding soft tissues. The tumor is nonosteogenic, arising from reticular elements of the bone marrow. The appearance histologically may be simulated by anaplastic carcinoma, lymphosarcoma and Ewing's tumor, but the diagnosis is based on the demonstration by special staining of an excess of reticulin.

Roentgenogically, the tumor is found most often in the long bones, especially those of the lower extremity. The most common and constant change is a patchy destruction of the affected bone with an ill-defined boundary. In over 50 per cent of cases, there is a simultaneous development of patchy new bone formation within the involved area, giving rise to a mottled appearance. There is a tendency for the lesion to develop in the metaphyseal regions, but as with other malignant tumors, the epiphyseal line is respected. Usually the primary growth spreads endosteally. Periosteal new bone formation is seldom prominent but when present it is of a lamellated type. Progress of the disease is slow, with marked bone destruction, remaining localized for a long time. Eventually regional lymphodes are involved and distant metastases may appear in the skeleton, skin and subcutaneous tissues. Most of the tumors are very radiosensitive, the response beginning within one to three months. The affected bone shows varying degrees of sclerosis or "scar" bone formation, or occasionally an appearance very close to that of normal bone results.—*Samuel G. Henderson, M.D.*

RADIOISOTOPES

Palmer, Richard E. (Alexandria, Va.), and Leffler, Harrison H. (Washington, D. C.) The correlation between the uptake of I^{131}, protein-bound iodine and cholesterol levels in normal and abnormal thyroid states. *South. M. J.*, Dec., 1956, *49*, 1412–1420.

Serum cholesterol values (method of Bloor), protein-bound-iodine (PBI) determinations (chloric acid digestion technique), and twenty four hour percentage I^{131} uptake studies were compared in clinically normal and abnormal thyroid states.

In 115 euthyroid individuals, normal values by I^{131} uptake study and PBI determination confirmed the clinical impression in a very high percentage of instances. A combination of the 2 procedures proved even more accurate. Cholesterol studies were abnormal in such a high percentage of cases (25 per cent), that this procedure appeared of little value. I^{131} and PBI studies were about equally valuable in hyperthyroidism and hypothyroidism, and again cholesterol levels were found unreliable.

I^{131} proved the best laboratory aid in thyroiditis. In each of 3 cases, percentage uptake I^{131} was markedly diminished, and in 2 cases in which a differential count of the involved and uninvolved lobes was done, a striking decrease in activity of the diseased lobe was noted. I^{131} and PBI were of about equal value in diffuse goiter (8 cases) and PBI appeared to be a slightly better laboratory aid in nodular goiter (10 cases).

Twenty three cases referred because of obesity or weight gain and clinically euthyroid showed no evidence of hypothyroidism by I^{131} or PBI studies. Of 12 patients with weight loss thought to be euthyroid, PBI and I^{131} determinations fell in the range of normal in most instances. Of 13 cases presenting with menstrual irregularities, most fell in the normal range by both PBI and I^{131} studies and only one showed an abnormality (minimal decrease) in both studies.—*John T. McLelland, M.D.*

Adams, D. D., and Purves, H. D. The change in thyroid I^{131} content between 8 and 48 hours as an index of thyroid activity. *J. Clin. Endocrinol. & Metabol.*, Jan., 1957, *17*, 126–132. (From: The Endocrinology Research Department of the New Zealand Medical Research Council, Medical School, Dunedin, New Zealand.)

Eight hour, 24 hour, and 48 hour thyroid uptake of I^{131} and 48 hour urine I^{131} measurements were per-

formed on 31 patients with hyperthyroidism and 35 euthyroid patients.

It is found that the spread between the 8 hour values in hyperthyroid and euthyroid patients is greater than at 24 hours. Also that the 8–48 percentage I^{131} thyroid uptake change rate is superior to the 8 hour measurement in separating hyperthyroid patients from euthyroid patients, there being overlapping of 3 hyperthyroids in the former as compared to 6 in the latter. The 48 hour urinary I^{131} is recommended to detect extrathyroidal sites of I^{131} accumulation.

It is therefore suggested that the 8 hour thyroid uptake is superior to the 24 hour uptake, the 8–48 hour study is superior to the 8 hour uptake alone, and the 8 hour uptake, 48 hour uptake and 48 hour urine measurements should be routine in thyroid function studies.—*George Roberts, M.D.*

Oliner, Leo, Kohlenbrener, Robert M., Fields, Theodore, and Kunstadter, Ralph H., with the technical assistance of Goldstein, Dolores R. Thyroid function studies in children: Normal values for thyroidal I^{131} uptake and PBI^{131} levels up to the age of 18. *J. Clin. Endocrinol. & Metabol.*, Jan., 1957, *17*, 61–75. (From: The Radioisotope Laboratory, Department of Metabolic and Endocrine Research, and the Department of Pediatrics, Michael Reese Hospital, Chicago, Ill.)

Thyroid I^{131} uptake and serum PBI^{131} studies were performed in 73 children between the ages of two and one-half months and eighteen years; 61 of these children were clinically deemed to be normal regarding thyroid function and 12 were abnormal. Methods for administration and measurement are described. Similar studies on 64 euthyroid adults are included for comparison.

Thyroid I^{131} uptakes in children are in the same range as are those of adults.

Serum PBI^{131} values were significantly elevated in the one to four year age group, and the mean was higher than normal from five to nine years of age. This suggests a state of thyroid "hyperactivity" through the age of four years and possibly up to the age of age nine years.—*George Roberts, M.D.*

Beiler, D. D., and Love, W. H. Thyroid function in Legg-Perthes disease. *J. Bone & Joint Surg.*, Dec., 1956, *38-A*, 1320–1322. (From: Departments of Radiology and Orthopaedic Surgery, George F. Geisinger Memorial Hospital and Foss Clinic, Danville, Pa.)

Thyroid function in 10 cases of unilateral Legg-Perthes disease was studied by means of clinical examination, chemical serum protein-bound-iodine determination, twenty four hour I^{131} uptake, salivary I^{131} concentration (in 7 of the 10 patients) and surface mapping of I^{131} uptake.

The study group was composed of 4 females and 6 males. Duration of the disease varied between six weeks and twenty-two months, and age between four and fourteen years. Five patients were considered in the regenerative phase of the disease process and 5 in the degenerative phase.

All 10 patients fell in the normal thyroid activity group by clinical examination and twenty-four hour I^{131} uptake studies. All 7 patients tested had normal I^{131} salivary excretion.

Three of the 10 patients showed slightly increased protein-bound-iodine levels, which on repetition five months later without intervening drug therapy fell within the normal range. Surface scanning showed asymmetric activity in the gland in one of these patients and in a second patient who was normal by all other methods of examination.

The results in this study give no indication of a relationship between Legg-Perthes disease and an abnormal thyroid state.—*John T. McClelland, M.D.*

Paine, Robert. (St. Louis, Mo.) Results of treatment with radioactive iodine in heart disease. *South. M. J.*, Dec., 1956, *49*, 1451–1458.

Forty-one cardiac patients were given radioactive iodine as palliative therapy, and results were evaluated in terms of improvement in symptoms of angina pectoris and congestive heart failure. Thirty-two of the patients had angina pectoris. Seventeen had congestive heart failure. The majority of patients were given 25 millicuries I^{131} as a single dose or (and preferably) 3 doses of 10 millicuries I^{131} spaced at one week intervals.

A significant reduction of symptoms following therapy occurred in 27 of the 32 patients in the angina pectoris group and 8 of the 17 patients in the congestive failure group. Improvement generally became noticeable between one and six months following therapy. Nitroglycerin rquirements were appreciably reduced in the angina pectoris group, but clinical improvement in the congestive failure group was not followed by a decreased need for digitalis, diuretics, or salt restriction.

Improvement was not related to inital basal metabolic rate or protein-bound-iodine levels, nor to the primary etiology of the heart disease. There was, however, a close correlation between the response to therapy and the effect of therapy in reducing the basal metabolic rate. A drop in protein-bound-iodine level, rather than the initial protein-bound-iodine level, also was correlated with improvement in the few patients evaluated by this test.

Twelve patients showed varying degrees of symptoms related to hypothyroidism and this was controlled as appeared necessary by small doses of

thyroid extract. In 2 patients showing progressive cardiac decompensation, therapy possibly accelerated the downhill course.

The author concludes that radioactive iodine is an effective palliative agent in the treatment of heart failure and angina pectoris and most effective in patients whose disease is stable and not rapidly progressive.— *John T. McLelland, M.D.*

Ireton, Richard J., and Ullery, John C. The management of ascites with radioactive gold. *Surg., Gynec., & Obst.*, Oct., 1956, *103*, 437–442. (From: The Department of Surgery and the Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, Ohio.)

Thirty-five patients who received 38 treatments with radioactive gold were evaluated from the standpoint of control of ascites and pain. Apparently all received intraperitoneal instillations of radioactive gold. The patients were classified as to tumor type and also as to whether or not they had surgery or radiation therapy prior to, or following, gold therapy.

Results are tabulated in 3 groups of patients: complete remission of ascites, temporary remission, and no remission. In the first group consisting of 9 patients, 5 are alive for from two and one-half months to seventeen months with pain relief in the 4 patients who had pain. In the second group, a remission of at least six weeks was produced with relief of pain in 4 of the 6 who had pain. In the group without remission of ascites, there was relief of pain in 4 of 13 who had pain prior to therapy. Nine of 19 patients in group 3 were dead in less than six weeks, suggesting that the poor results in this group were due to the terminal condition of these patients.

Thus, one-fourth of patients had complete remission of ascites, one-half had temporary remission of ascites, and one-half had some pain relief. Prophylactic administration of radioactive gold is recommended by the authors.—*George Roberts, M.D.*

Orr, Louis M., Thomley, Miles W., and Campbell, James L. Distribution and concentration of radioactive Au 198 in inoperable prostatic cancer: Report of necropsy study. *J. Urol.*, Dec., 1956, *76*, 769–775. (Address: L. M. Orr, 1300 Kuhl Ave., Orlando, Fla.)

In this article the authors discuss the problem of the distribution and retention of radioactive gold following its injection into the prostate in the treatment of carcinoma. This information was obtained from studies of a patient who came to autopsy three weeks after the treatment of prostatic carcinoma with radioactive gold. On the basis of radioassays of the entire prostatic gland, there is evidence that a marked variation in the radioactivity of different parts of the injected tissue had occurred. In some areas of the gland there was six times as much radioactivity as in an area adjacent to it. This unequal distribution of radioactivity is partly corrected by cross-firing by gamma rays of radioactive gold, but certain parts of the tumor would receive no appreciable radiation from the beta particles. The latter irradiation effect would be localized in small foci throughout the prostate gland. While this might produce marked regression in the size of the gland, certain of the malignant cells would continue to remain viable. This was found to be the case when the tissues were examined microscopically.

The radioassay of other organs, three weeks after the treatment of the prostate with gold 198, showed that the greater portion of the injected material was present in the liver, spleen and bone marrow. The authors believe that in order to produce the desired level of radioactivity in the prostate gland, it will be necessary to use a more concentrated solution of radioactive gold.

In conclusion, the authors note that from the clinical standpoint the majority of the patients treated with radiogold injection of the prostate have shown improvement with marked regression of their primary lesion. Such favorable results have stimulated them to proceed further in an effort to find a better isotope and better methods of delivery of the isotope to the prostate gland.—*George W. Chamberlin M.D.*

Berry, N. E., and Burr, R. C. Intracavity irradiation of carcinoma of the bladder. *Canad. M. A. J.*, July 15, 1956, *75*, 93–97. (From: Queen's University and the Ontario Cancer Foundation, Kingston Clinic, Kingston, Ontario.)

The authors describe their technique for the intracavitary treatment of carcinoma of the bladder. They utilize a 25 mc pellet of radioactive cobalt measuring 6 mm. in length and 1 mm. in thickness placed in the tube of a Foley catheter, the bag of which is inflated with methylene blue, sodium iodide, and sterile water. Control of the position of the catheter is obtained roentgenographically and cystostomy is avoided. A dose of 4,000 r is given at each of 2 sittings, spaced four days apart with each sitting requiring two and one half days. This technique is used for all tumors other than those in the dome of the bladder where distortion due to the catheter tip might lead to inadequate dosage.

The method has been employed in cases where there have been numerous recurrences or where there have been so many lesions that it was impractical to resect them all and where they were not deeply infiltrating. Patients have had considerable reaction from this treatment with burning and frequency but these symptoms subside in two to three weeks. These lesions should be near the trigone or

side walls to receive adequate irradiation. Suprapubic cystotomy is performed only when the tumor is to be resected. Resection is, of course, the treatment of choice for single superficial lesions. In the far advanced infiltrating lesions, all available methods may have to be combined including supervoltage rotational or multiport therapy.—*Arch H. Hall, M.D.*

Yiannakopoulos, Apostoulos, and Scheer, Kurt Ernest. Der Einfluss von Protraheirung und Fraktionierung auf das Hauterythem bei Bestrahlung mit Sr^{90}. (The influence on skin erythema of protraction and fractionation of radiation with Sr^{90}.) *Strahlentherapie*, May, 1956, *100*, 165–168. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

The skin of the upper thigh and mid-abdomen of 5 persons was irradiated with doses from 500 to 5,000 rep from two Sr^{90} applicators. One applicator had an intensity of 4,400 rep per minute, the other 180 rep per minute. The protraction attained with the lower intensity source uniformly yielded less erythema than the same physical dose given with the high intensity plaque. Fractionation of the dose, as well as protraction, caused less intense erythema.—*Henry G. Moehring, M.D.*

MISCELLANEOUS

Levitt, W. M., and Oram, Samuel. Irradiation-induced malignant hypertension: Cured by nephrectomy. *Brit. M. J.*, Oct., 1956, *2*, 910–912. (Address: W. M. Levitt, Department of Radiotherapy, St. Bartholomew's Hospital, London, England.)

A man aged thirty-three had left orchiectomy for seminoma in 1941. A large mass developed in the upper abdomen, apparently mainly on the left, but extending well over the midline. The patient was given deep roentgen therapy in May and June, 1943. The left kidney region received just under 3,000 r, the right somewhat less, the field sizes and elapsed time not specified. Seven years after treatment his blood pressure was 150/90; two years later, 160/90; and one year later, 165/95. He then developed headaches which became progressively worse, causing him to seek medical advice one year after onset, eleven years after radiation therapy. His blood pressure was then 215/130, and he had retinal changes of Grade III–IV. The hypertension did not respond to medical management. The left kidney showed delayed dye excretion and decreased urine urea concentration, while the right was normal.

Left nephrectomy was performed, revealing general fibrosis of the perirenal stroma. The kidney showed arteriosclerotic changes, even though physical examination of the patient failed to reveal evidence of arteriosclerosis in the nonirradiated vascular system. In the first year after operation, the blood pressure gradually returned toward normal, and the fundi became completely normal. After two years, the patient was maintained free of symptoms on reserpine 0.25 mg. three times a day, with a blood pressure of 152/92.

This case history is reported because of the late manifestation of radiation damage, and the relief from the resultant malignant hypertension by nephrectomy.—*R. Kenneth Loeffler, M.D.*

Mallams, J. T., and Miller, J. E. Clinical experience with image intensification. *Radiology*, Dec., 1956, *67*, 877–881. (Address: J. T. Mallams, Southwestern Medical School, University of Texas, Dallas, Texas.)

The development of image intensification is briefly reviewed, and its usefulness in overcoming some of the shortcomings of conventional fluoroscopy is stressed. The unsatisfactory results of fluoroscopic observation are due to a deficiency of the human eye in observing low levels of brightness. Image intensification permits a greatly increased brightness of the fluoroscopic image without increased exposure of the patient. The chief advantage of the image intensifier is the fact that long periods of dark adaptation are no longer required. In addition, the increased brightness frequently permits acquisition of the desired information in a relatively short time so that less time is consumed in fluoroscopy with the image intensifier than in the conventional examination. Disadvantages of the procedure in its present stage of development are the high cost of the equipment and the small field size.

Image intensification has proved most useful in studies of the upper and lower gastrointestinal tract, myelography, and cardiac catheterization. Special applications in connection with other procedures, such as foreign body removal, uterosalpingography, venography, bronchography, and therapy localizations, are mentioned. It is the most important step in the development of cineradiography and will probably be the medium through which cineradiography will become available to the average physician.—*Harold C. Hamilton, M.D.*

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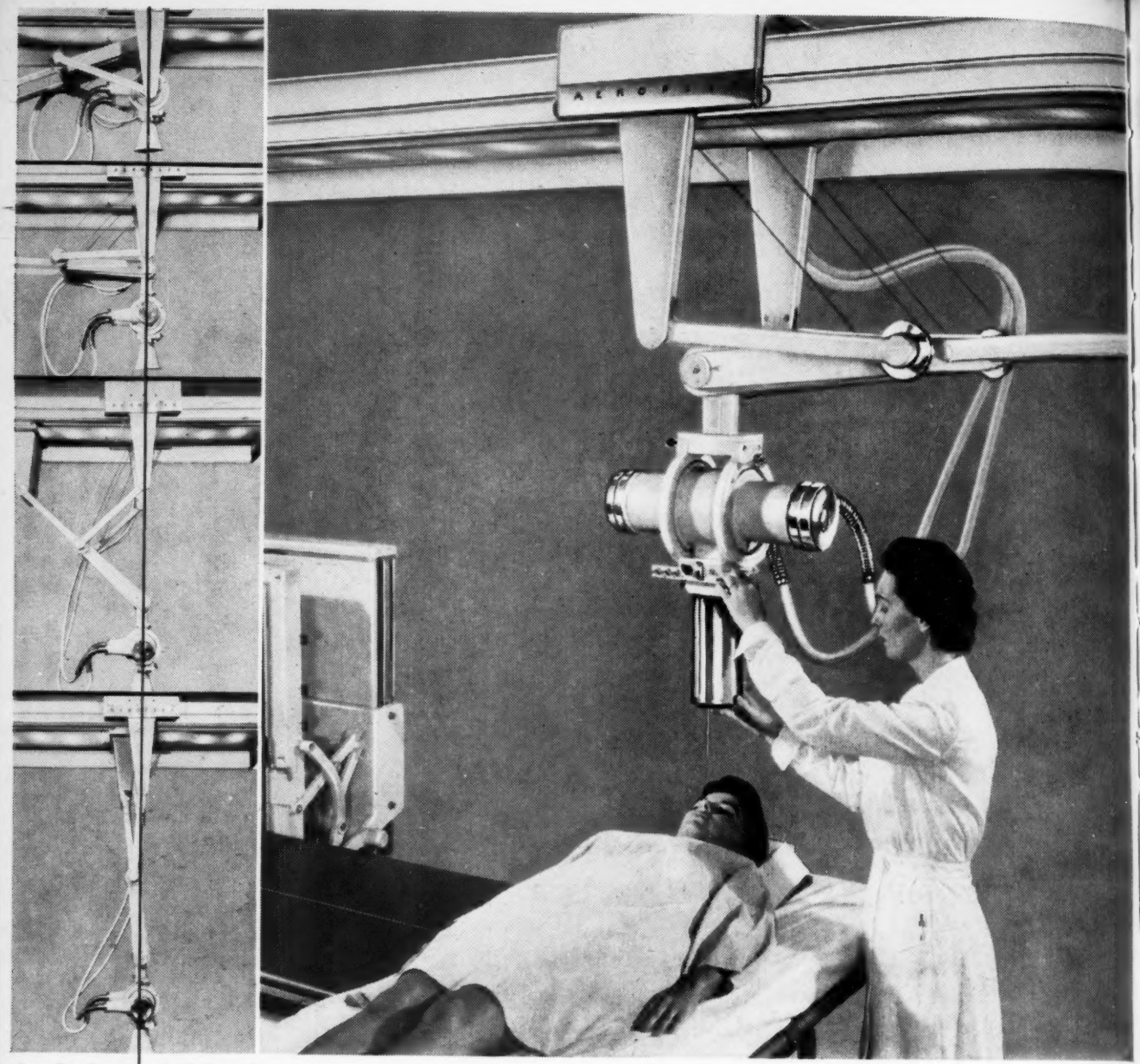
INDEX NUMBER



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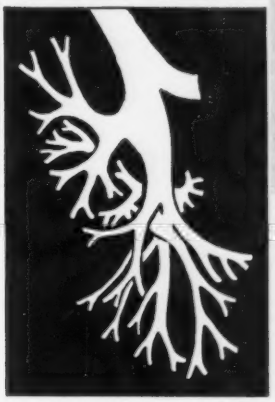

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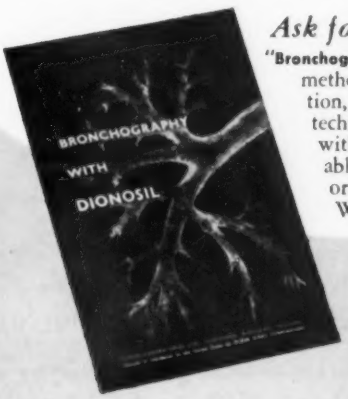

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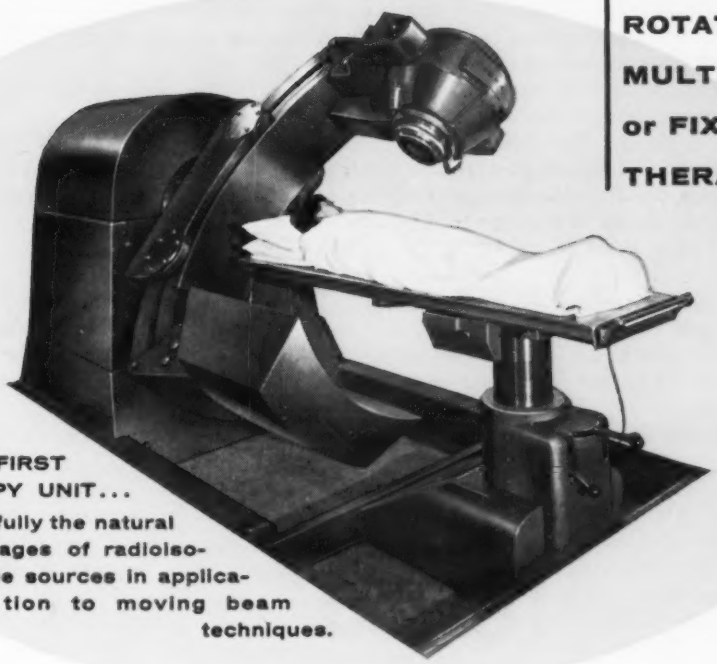

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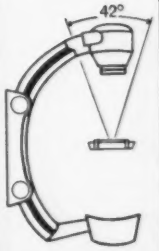

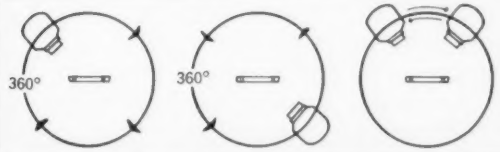

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1. Olcott, C. T., and Dooley, S. W. Agenesis of the lung of an infant. Am. J. Dis. Child., 1943, 65, 766–780

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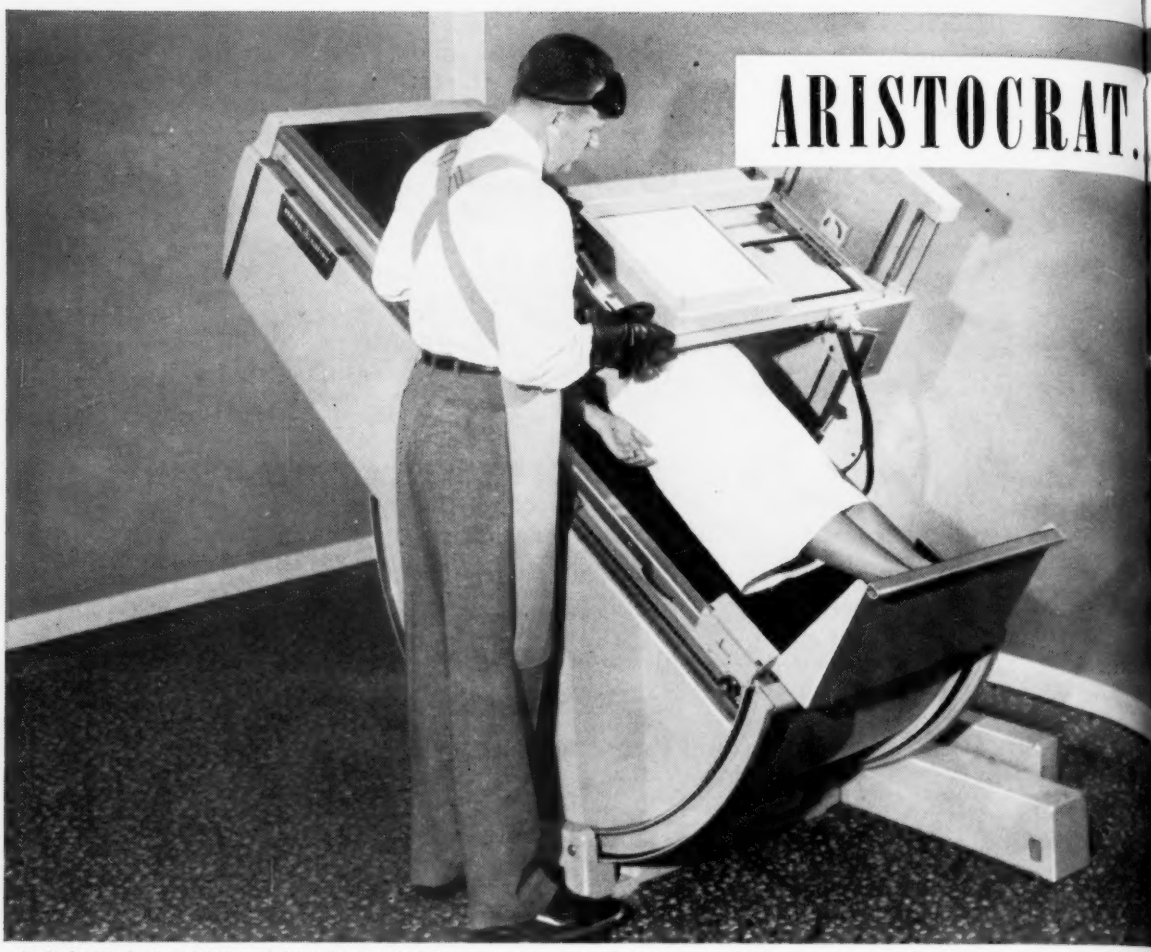

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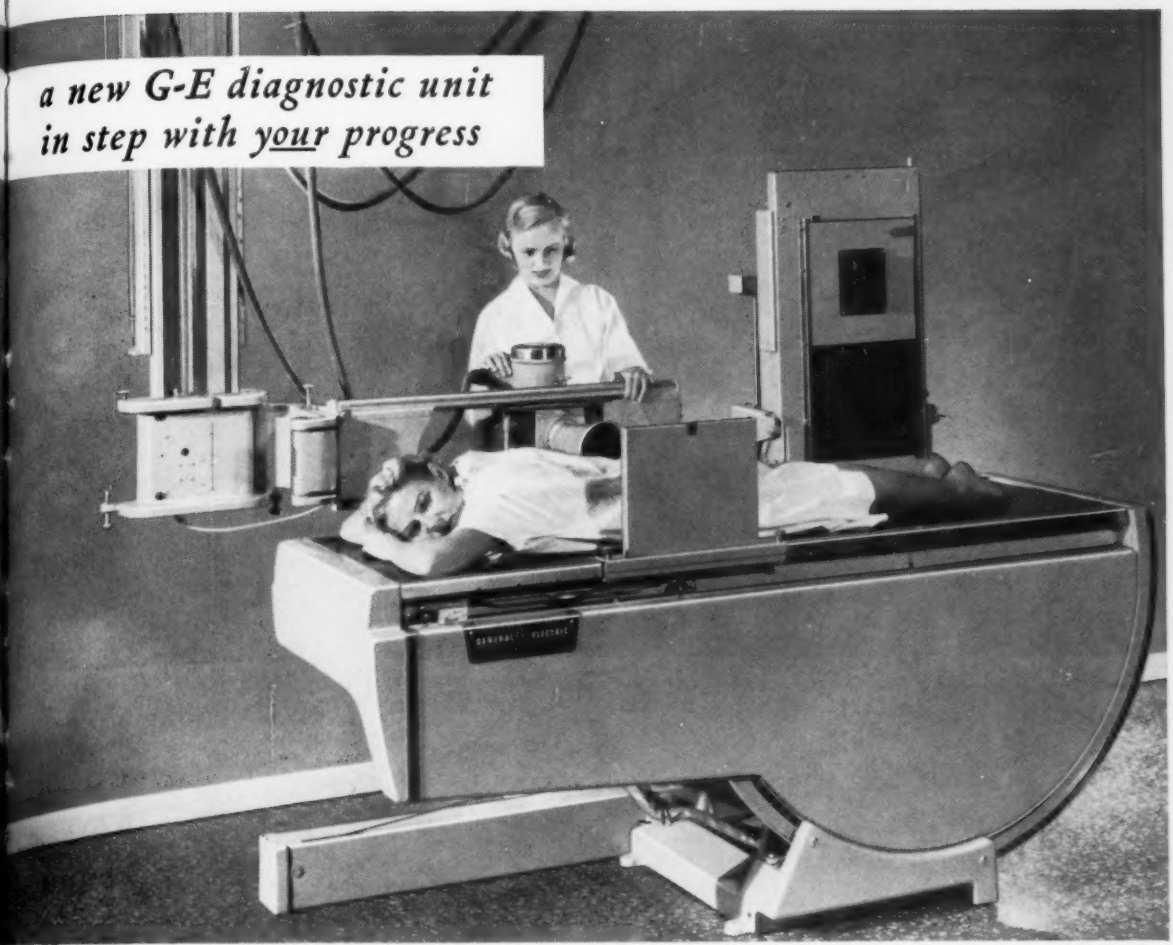

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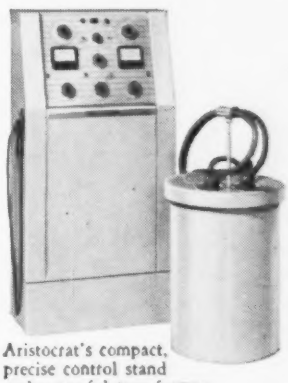

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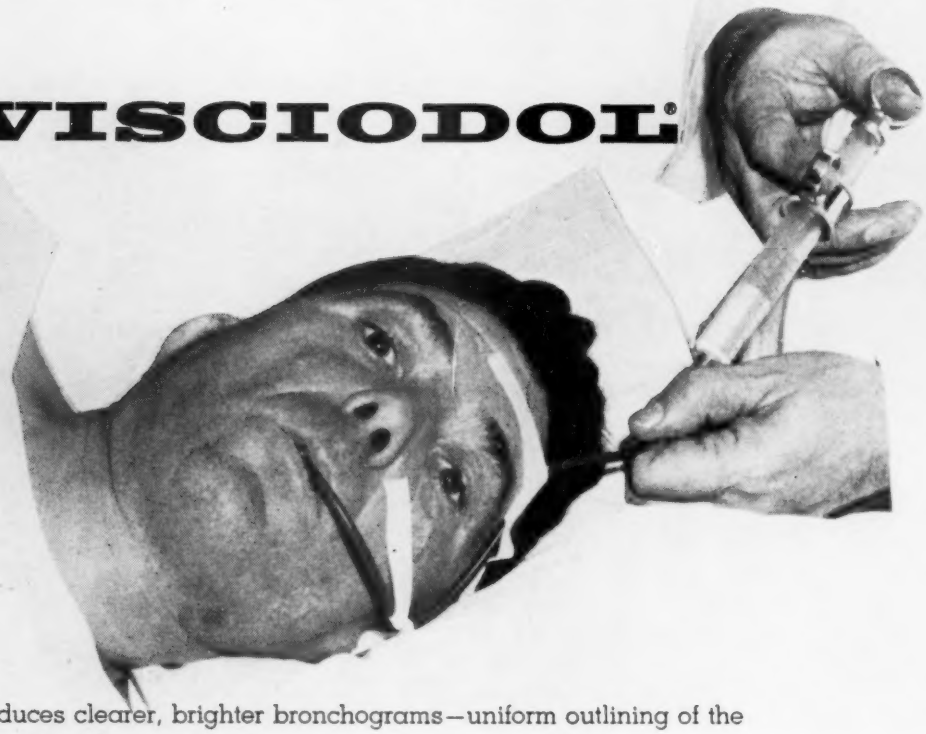

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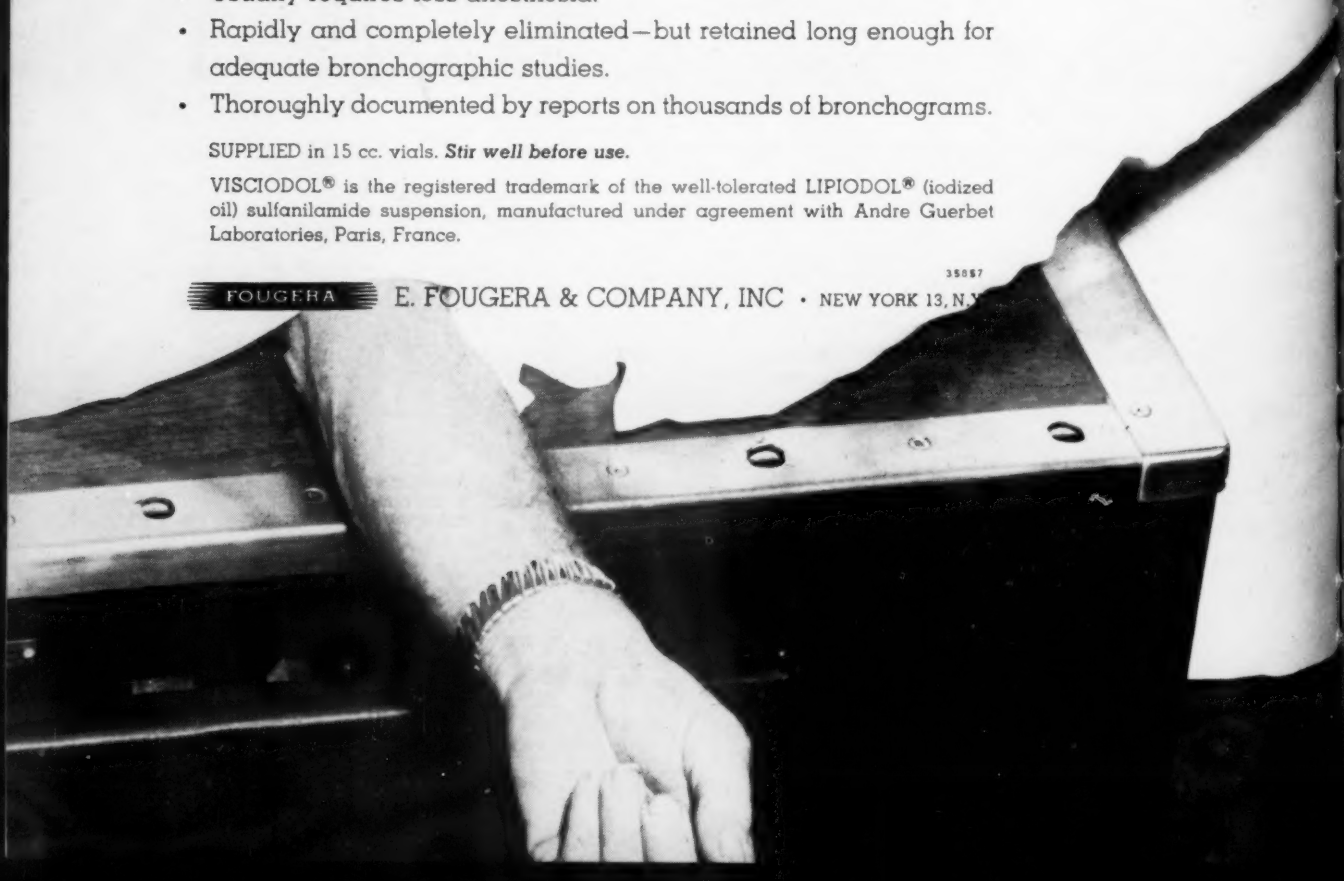

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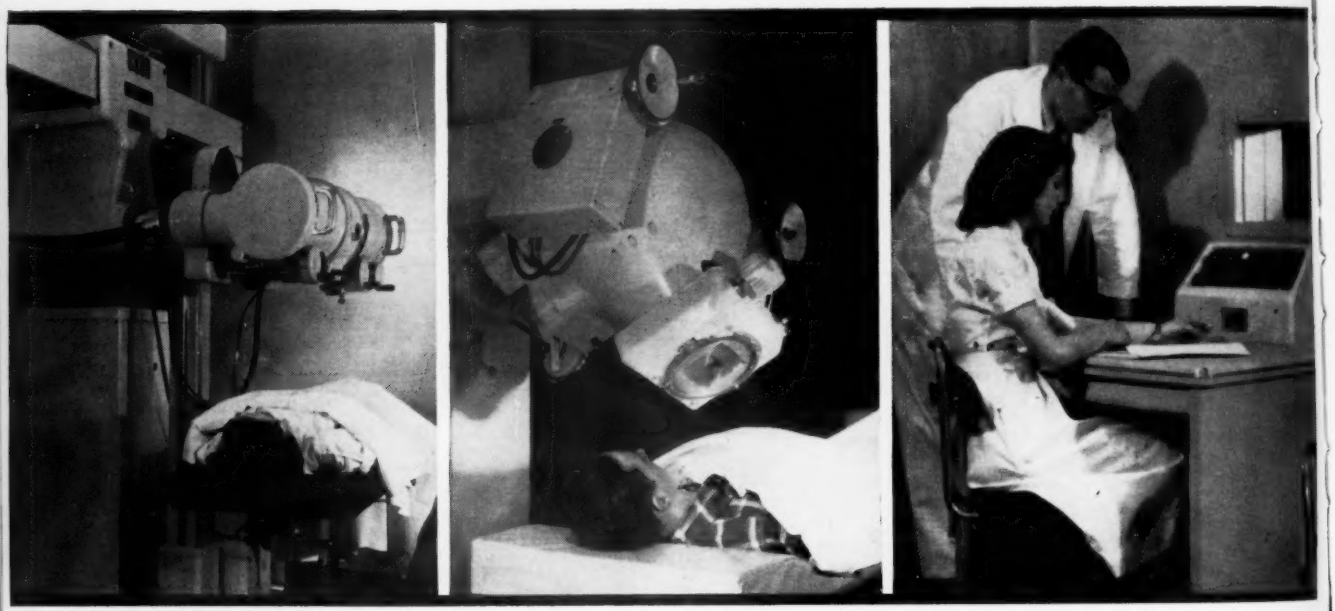

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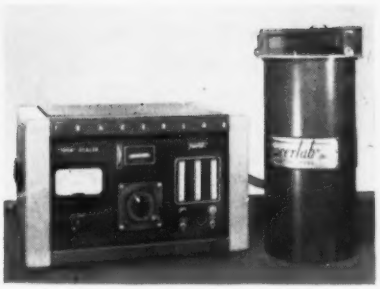

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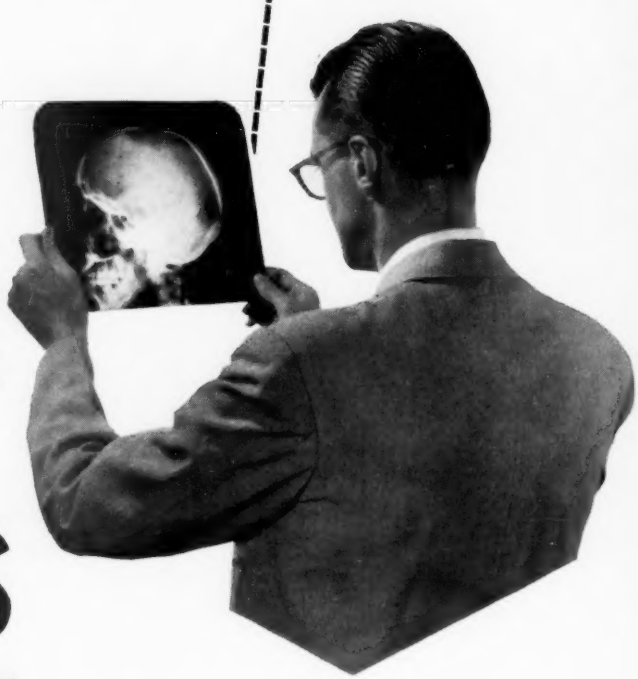

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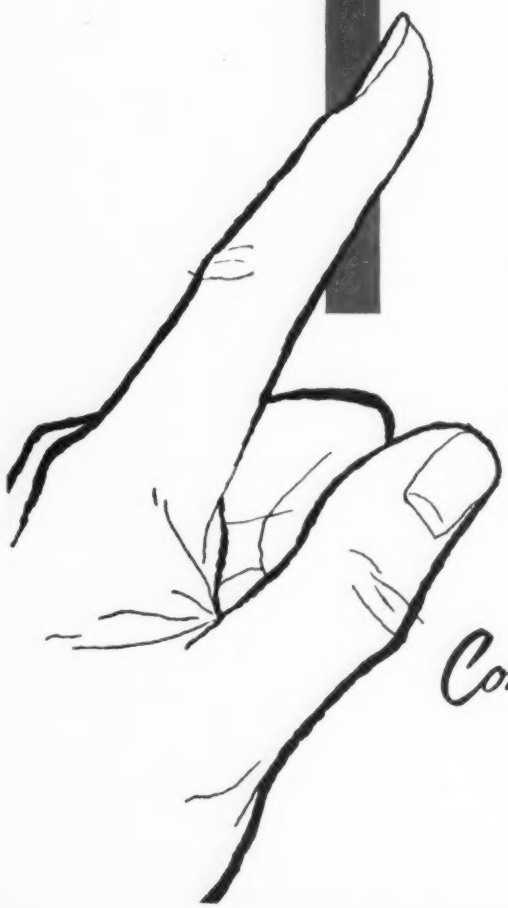

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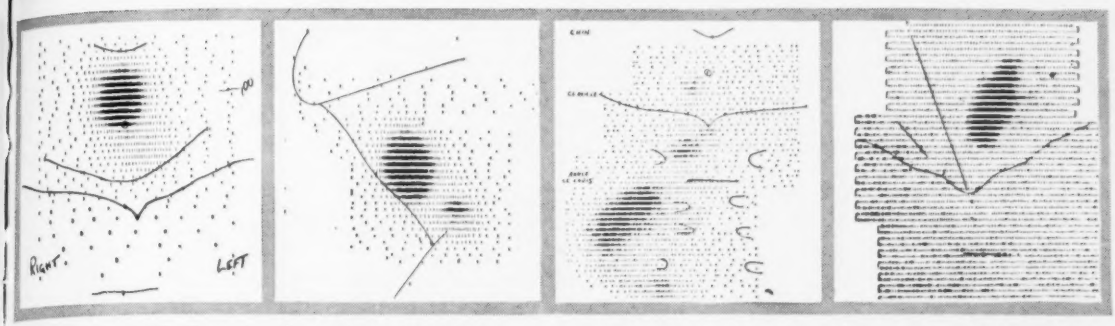

Thyroidectomy in 1928. Thyrotoxic symptoms in 1956. Scan shows recurrence in pyramidal region.

Same patient as at left. Left lateral view. Gamma-ray Spectrometer used for background reduction.

Intrathoracic recurrence 20 years after surgery. Gamma-ray Spectrometer used with Scaler.

Scan showing residual thyroid area following surgery and node dissection. Spectrometer not used.

Actual scans shown above illustrate typical diagnostic problems which lend themselves to the Isotope Scanner system. The three scans at the left were made using a Nuclear-Chicago gamma-ray Spectrometer-Scaler unit. This combination is considered the only valid and safe way to "erase" background and eliminate scatter, because it cannot erase even the weakest isotope concentration.

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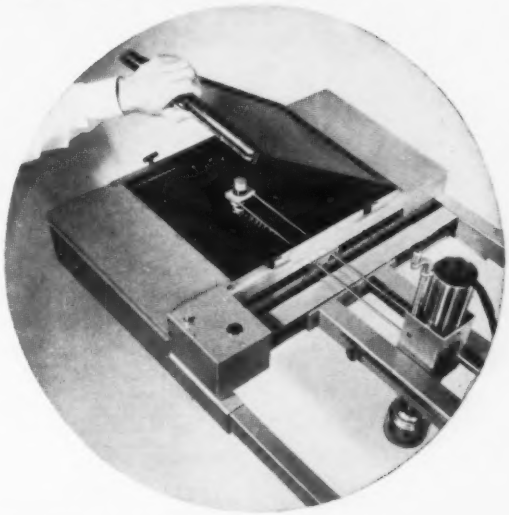

Reference: David E. Kuhl, R. H. Chamberlain, John Hale and R. O. Gotson: A High-Contrast Photographic Recorder for Scintillation Counter Scanning. Radiology, pgs. 730-739, May, 1956.

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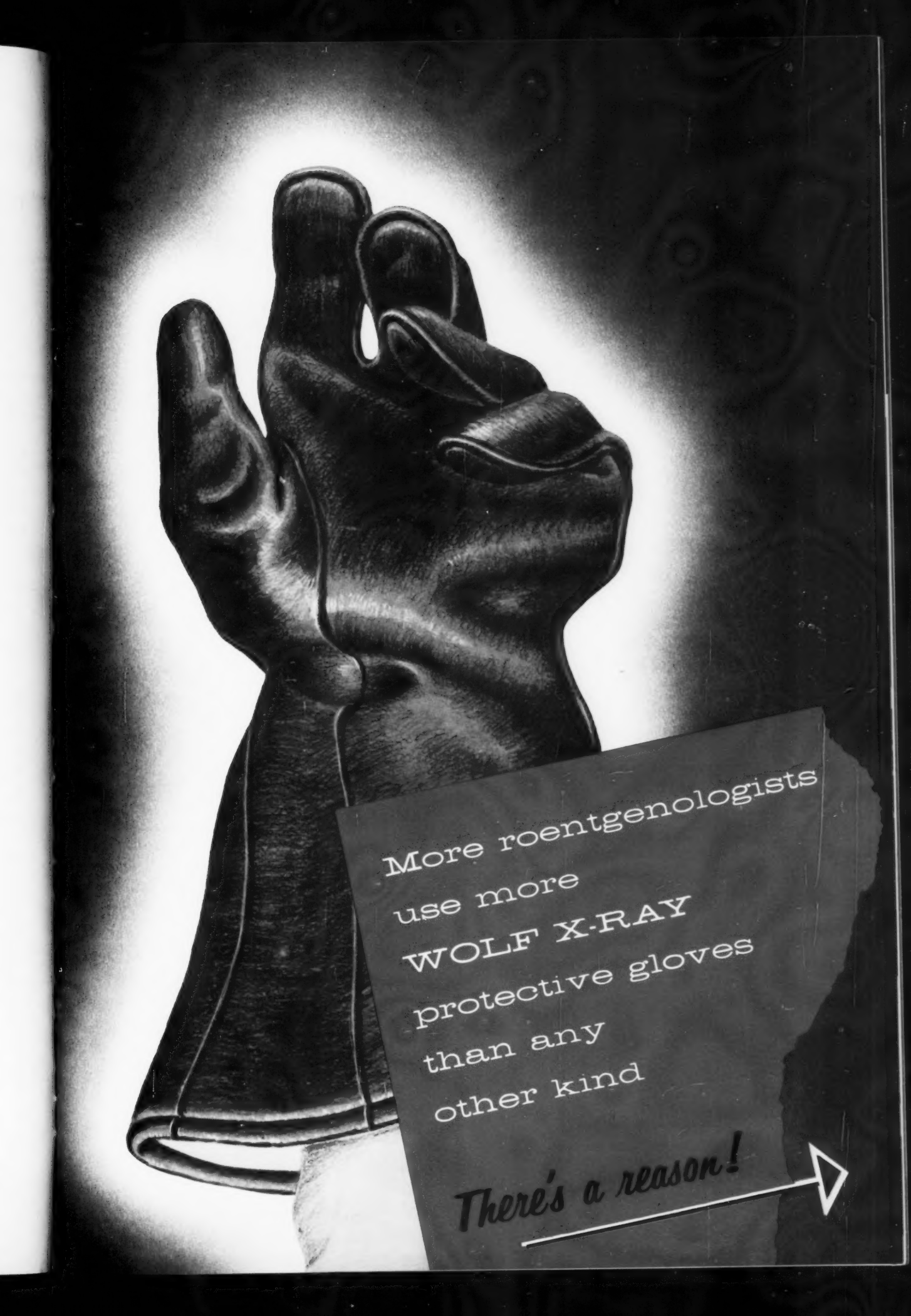
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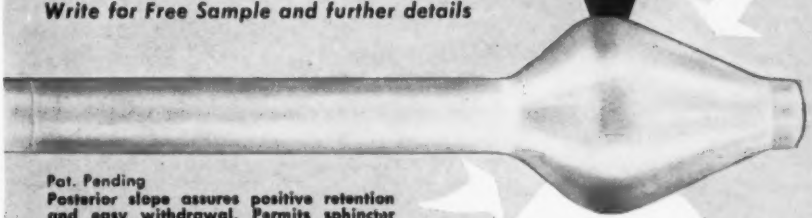

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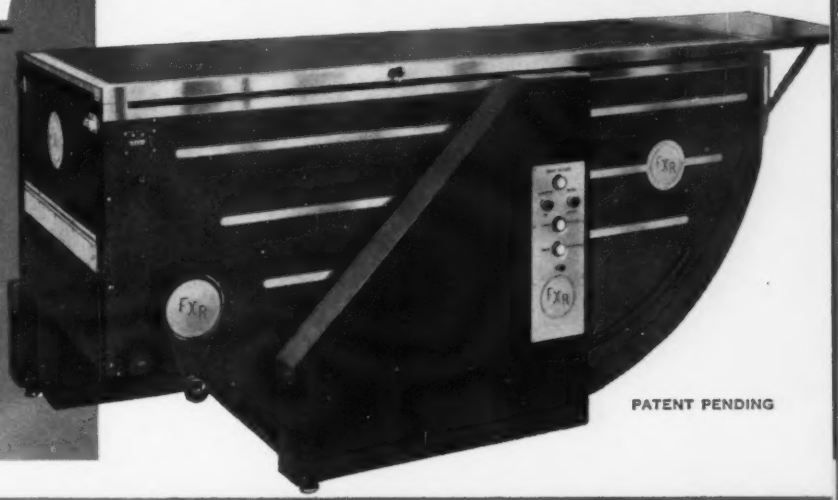

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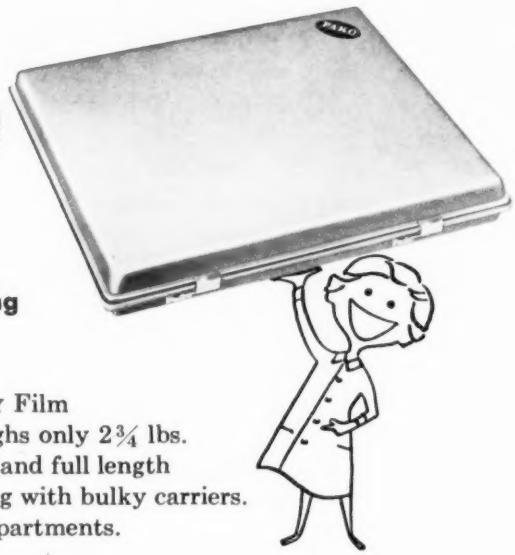

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10	1
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13	2
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15	3¼
16	4
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18	6⅔
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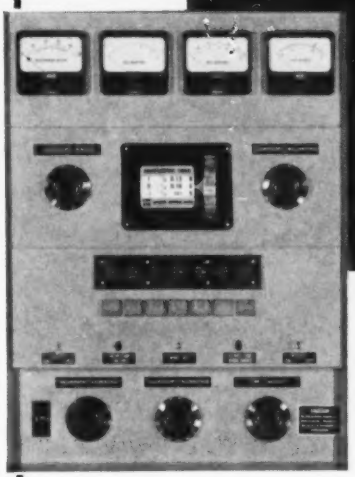

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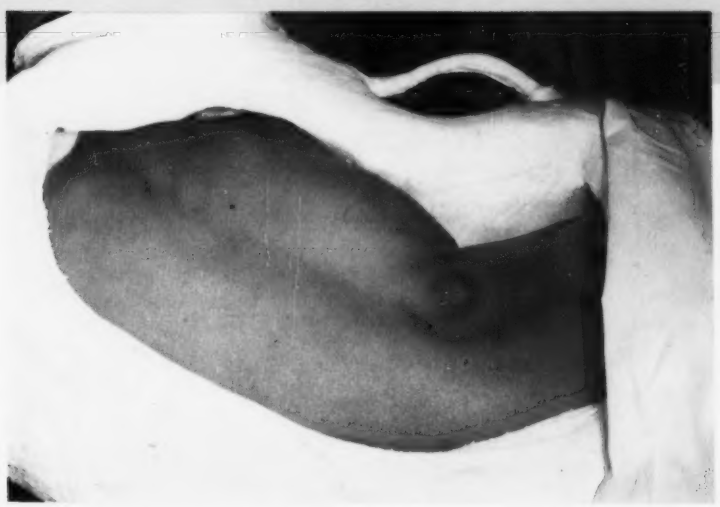

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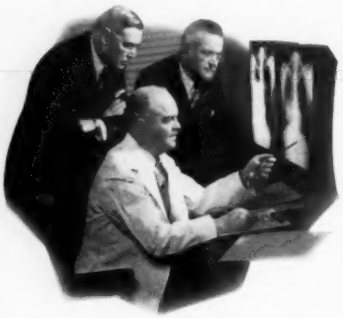

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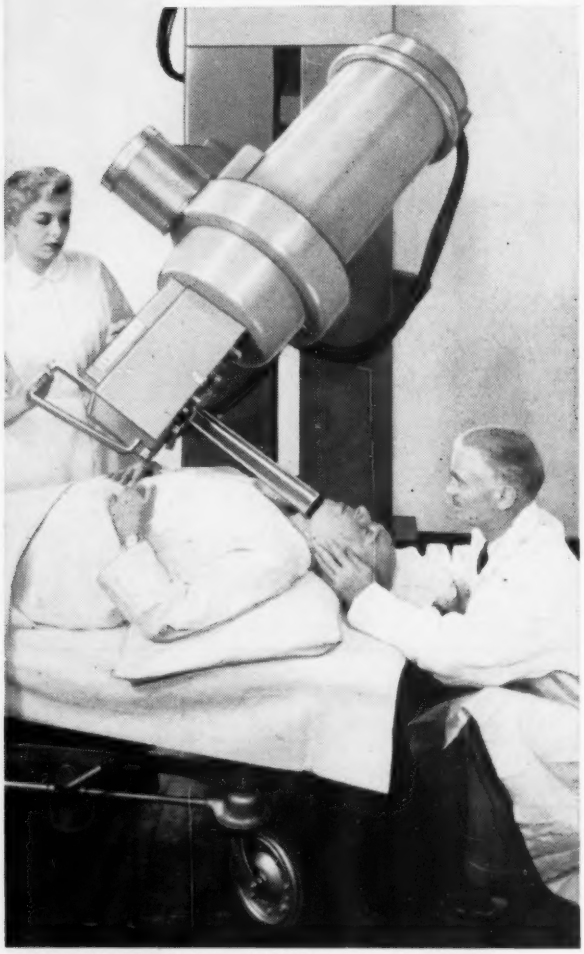

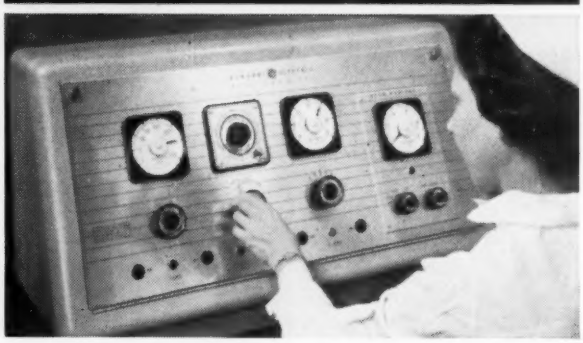

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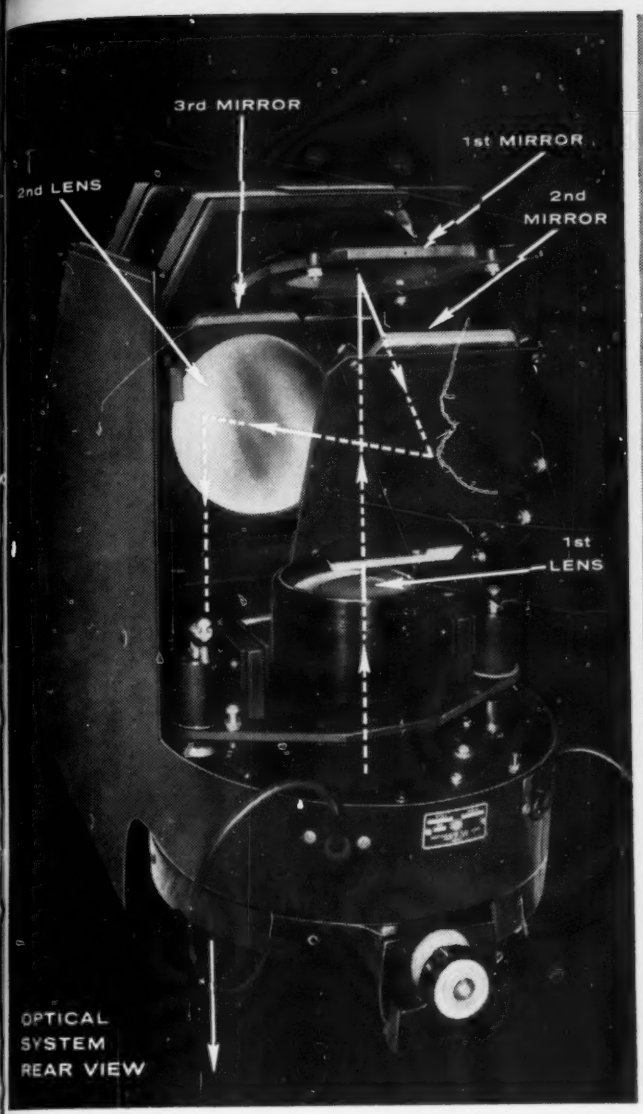

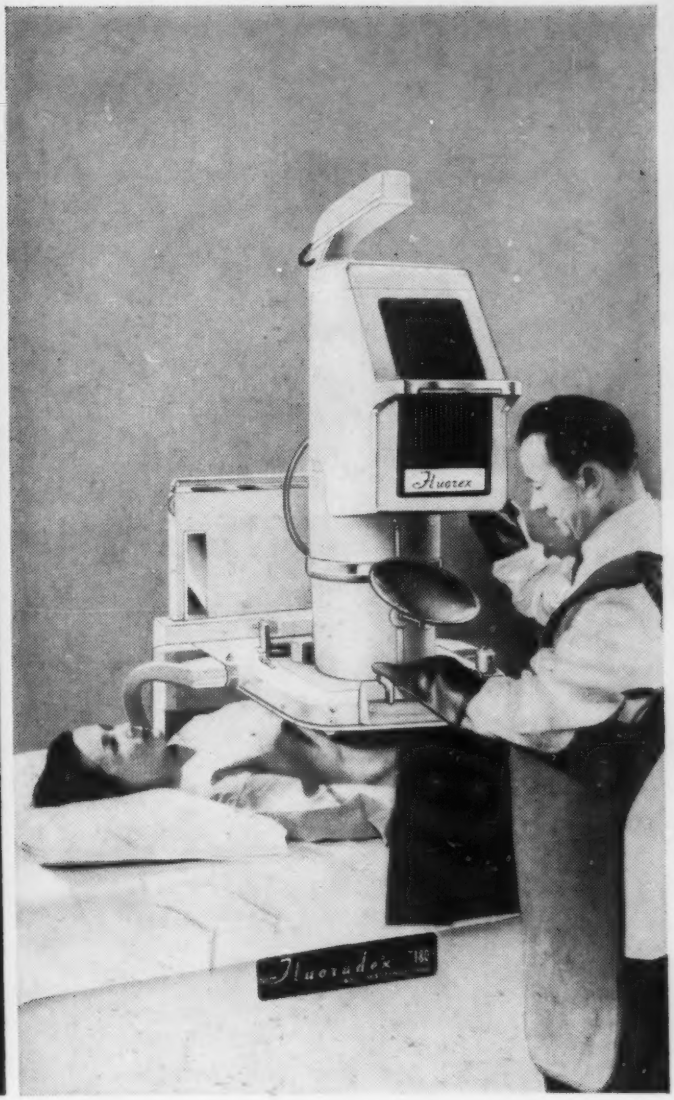

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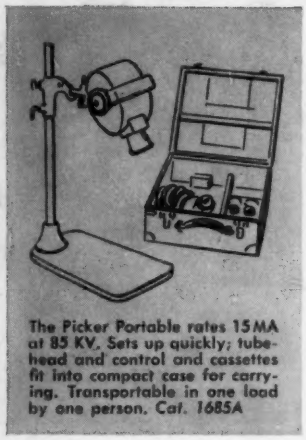

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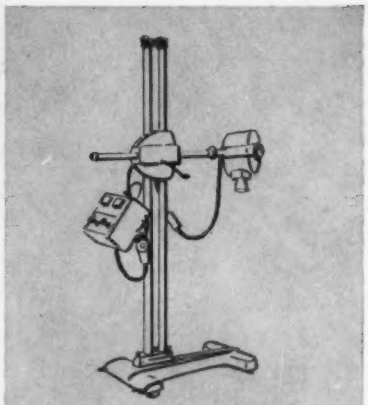

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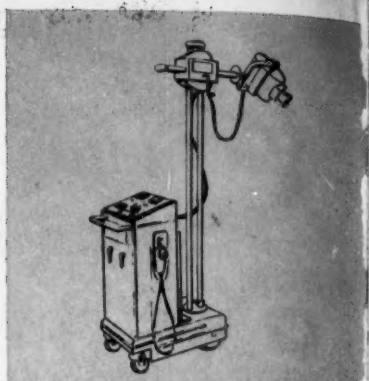

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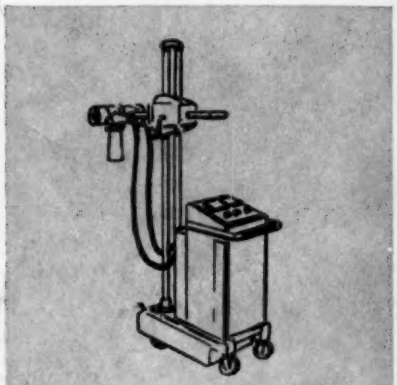

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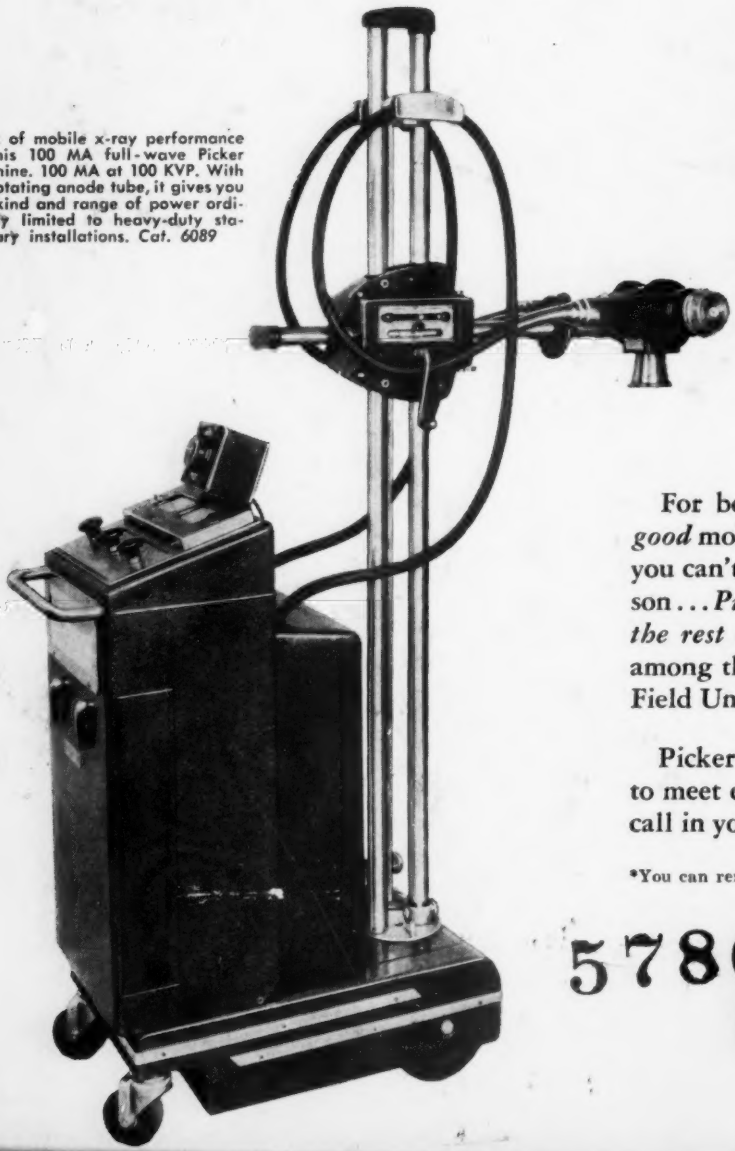

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